The American Journal of Human Genetics

Vol. 10 No. 3 *September 1958*

Sir Archibald Garrod's "Inborn Errors of Metabolism"

III. Albinism

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"The suggestion, which we would make for the consideration of the physiologist, is that the ultimate difference between the normally pigmented individual and the albino will be found after all to be one of *structure*. It is easier to grasp the influence of a difference of gametic constitution on structure than on chemical process." *A Monograph on Albinism in Man*, Pearson, Nettleship and Usher, 1911.

INTRODUCTION

THE INCLUSION OF ALBINISM in the list of inborn errors of metabolism in 1908 must be ascribed to Garrod's intuitive genius. Certainly the evidence available to him at that time was not convincing. Nor did his concept appeal to Pearson, Nettleship and Usher (1911) who wrote the above quotation three years later in the midst of the most complete survey of albinism ever attempted. Until then the appropriate data had not yet been collected to show whether albinism was an acquired disease, an arrested development or an hereditary defect of some kind. The condition was known, of course, from ancient times, and its ready diagnosis and sharp segregation should have marked it for early study. Pearson did choose it as a test case of the applicability of Mendelianism to man. His method was a monumental compilation of all known references, pedigrees and pictures of albinism of all grades in man and animals. All work on albinism must now start with this monograph, even though the study included an enormous variety of pigmentary defects, both hereditary and acquired. It was left for the later investigators to define universal complete albinism as a separate entity among the many disturbances of pigmentation, and to prove its transmission by a single autosomal recessive gene. Only now are the mysteries of pigment cell metabolism with its additional variations through physiological control beginning to be laid bare. Contrary to the popular impression, our understanding of albinism as an inborn error of metabolism is still incomplete. Yet the hope perseveres of confirming Garrod's remarkable insight that albinism is an inherited lack of an enzymic step in pigment production.

I. CLINICAL DESCRIPTION AND DEFINITION

The striking appearance of the complete albino is familiar to almost everyone. We owe most of the clinical observations on albinism to dermatologists and opthalmolo-

Received May 28, 1958.

* This laboratory is supported by U. S. Public Health Service Grant A567 and by U. S. Atomic Energy Commission Contract No. AT (30-1)-901 with the New England Deaconess Hospital.

gists, who deal for the most part, with the same readily apparent external abnormalities that the layman sees. From such a viewpoint the many varieties of deficient pigmentation tend to be classed with complete albinism, even though the relationship is only assumed and superficial. This has led to oversimplification of the problem of albinism as one concerned with the simple presence or absence of pigment. With the assumption of some relation between the various types of pigment deficiency, whether in man or animals and in hair, skin or feathers, goes the single greatest barrier to the understanding of albinism. For this reason, consideration here will be limited to the simplest, most pronounced, and most unmistakeable type, complete albinism. Information derived from studies on other kinds of abnormal pigmentation will be adduced explicitly so far as possible, and only for what insight they may give into complete albinism. Some of these other varieties will be described before attempting a definition of complete albinism.

Varieties of Pigmentary Deficiency: People of all races are seen with deficient pigmentation present at birth or developing later in life. The late developing forms range from early graying of hair to localized areas of depigmented skin and hair that follow injury and inflammation (vitiligo) or that occur spontaneously over wide areas (leucoderma). While it cannot be said that heredity plays no role in the production of these deficiencies, interest is greater in those forms present from birth (or from the earliest age when they can be noted, since pigment accumulates with age). Such congenital forms include well-demarcated patches centered more or less symmetrically somewhere along the median line of head or abdomen (white locks and "spotlings"), and the quite separate piebald markings which do not have this center of symmetry. The inheritance of these is usually dominant (Gates, 1946), and they may be remarkably constant in location, if not in size throughout a pedigree. If the areas affected are sufficiently large, the condition is frequently classed as "partial albinism", which is an unfortunate term that causes confusion. It must, for example, be distinguished from "incomplete albinism," in which some small residues of pigment can be found in the affected areas of an albino.

Ocular albinism is a precisely defined anomaly which has been seen in a limited number of families, and is not associated with complete albinism even though the eye is affected in the same manner in both conditions. Ocular albinism is sex-linked. The affected males show the usual findings of the albinotic eye, with fair or normal coloration elsewhere. The heterozygous females can be distinguished regularly by a granular clumping of pigment in the periphery of the fundus (Falls, 1951, 1953; Francois & Deweer, 1952; Ohrt, 1957).

Incomplete Albinism: Less common than complete albinism are individuals who show traces of pigment. They have cream-colored or yellow hair and yellow or blue irides. Such individuals may occur more commonly among the heavily pigmented races, and have been called "xanthous" or "rufous" as well as incomplete albinos. They are unmistakably albinos, nevertheless, and they are probably only an arbitrary class of the "complete" albino (Pfandler, 1950). Examples were described by Franceschetti (1930) and Waardenburg (1932). As Pearson *et al* (1911–13) first observed, proof is never available that the universal complete albino is everywhere lacking in all pigment. The existence of this slightly pigmented group warns us not

to expect any absolute defect in the albino. Especially is this so when coupled with evidence that many albinos have some pigment at autopsy and even accumulate pigment during life. The amount may not be noticeable, but sufficient accumulation to ameliorate the visual difficulties is often expected by the practicing opthalmologist.

Universal Complete Albinism: Geoffrey Saint Hilaire in 1832 described "perfect albinism" (quoted by Pearson *et al* (1911)). He was the first to distinguish this type from "imperfect" and "partial" types:

"The skin and all the hair are milk white, sometimes yellow white. The iris and choroid, like the skin, are entirely *or almost entirely* deprived of coloring matter; so the iris is ordinarily rose or red, sometimes bluish or a pale or yellowish gray. The pupil, in place of black, is a bright red, little different from the color of fire". The italics have been added to emphasize the existence, referred to above, of undoubted albinotic individuals who possess some slight degree of pigmentation. To this description should be added the usual ocular accompaniments of defective vision, photophobia, nystagmus and ametropia (near- or far-sightedness plus astigmatism).

Albinos with some slight pigmentation and the "rufous albinos" with diffuse red pigment instead of granular black pigment are undoubtedly confused with the very fair individuals who occur among North European stocks, and with individuals having very widespread depigmentation of localized origin. An additional criterion besides that available from the superficial impression is needed to make such distinctions. Until we have one based on the knowledge of the disease mechanism, a somewhat arbitrary distinction must be accepted. In practice the distinction has usually been made on the basis of the visual defect. If this were present to any degree, the condition is classified as albinism. Such borderline cases are not too common, however. Pearson *et al*, believed there was a more or less gradual transition from complete, through incomplete, to partial albinism (white locks and piebaldism), yet they had no great difficulty in classifying 528 of their sibships as examples of complete albinism and 279 as incomplete and partial albinism. Complete albinism, recognizable superficially as an (essential) absence of pigment from the hair, eyes and skin, therefore makes up a relatively common although a purely descriptive, group of the pigmentary deficiencies in man (Fig. 1).

The great variety of other conditions that have been associated with albinism demands that the classification introduce some simplification. To this end, the many transitional forms and the associations with other anomalies have been omitted (see Busti-Rosner, 1956). Albinism is not necessarily associated with any other abnormalities save those referable to absent pigment. The visual defects may result entirely from the depigmentation. Despite the frequent allusions to macular degeneration and reduction of the retinal nerve layer, few of the albinotic eyes examined have had such pathological changes (Nettleship, 1906). Waardenburg (1932) and Franceschetti (1930) give later studies which have been made on albinotic eyes. Healthy, intelligent and long-lived albinos are well-known. The physician Sachs, who in 1812 described himself and his albinotic sister in a monograph ("Historia naturalis duorum leucaethiopum auctoris ipsius et sororis ejus") was one of these. There is a natural tendency to describe as separate entities albinism associated with

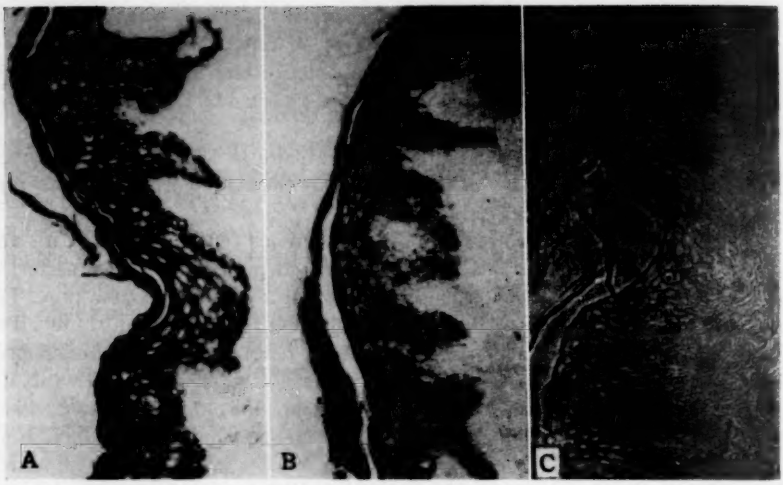

FIG. 1. Negro (A), Caucasian (B) and albino (C) human skin sections treated with Fontana silver stain. Note the relative amounts of melanin (argentophil granules) normally in the basal cells and diffused through the epidermis (from Young, 1957).

minor peculiarities in a single individual or in a single family. It has not been emphasized before that the fraternities most likely to contain albinos, i.e. those from consanguinous matings, are also prone to contain other recessive conditions, and that many of the abnormalities recorded as associated with albinism may be present on this basis. It can be stated that there are no known constant associations of albinism with other specific abnormalities and that many of the associated conditions that have been described were incidental. The possibility remains that within the descriptive group of complete albinism there exists a number of genetically distinct conditions each with its own peculiar syndrome. Only genetic analysis could at present reveal such types by their "breeding true".

Limiting our consideration to the one certain form of albinism has considerable heuristic value. Any progress made in understanding it will help with understanding the other forms. But the interplay works both ways. There was a positive value in Pearson's indiscriminate collection of information on all forms of pigment defect:— "All grades of pigmentation, all changes of pigmentation, and all local absences of pigmentation are of peculiar interest to the student of albinism. Above all, it is important to indicate any links which may occur between these classes of phenomena." (Pearson *et al*, Part I, p. 197).

II. GENETIC HISTORY

The earliest tales about albinos implied that the condition was hereditary. One of the most widespread of myths, comparable to those of Atlantis and of the Amazons, speaks of a race of albinos who remained hidden from the light during the day but at night could see to race swiftly through the forests. Linnaeus accepted Pliny's

version of these people, and they appeared in the first twelve editions of his *Systema* as *Homo nocturnus*. Confirmation of a sort was given this myth when localized areas in the world were found where the incidence of albinism was unusually high. The most famous of these, but by no means the only one, is the Caribbean area inhabited by the San Blas Indians, where an incidence of albinism of 7 per 1000 was found (Harris, 1926). In general, however, the geographic distribution reported by Pearson *et al* was fairly uniform in different climes and among different peoples and amounted to a world-wide incidence of about 1 in 20,000. The possibility that the heterozygote has some advantage in certain environments should not be overlooked as an explanation for the localized departures from this mean incidence.

With the background information provided by the myth of the albino race it may seem curious that scientific opinion should have erred so grievously for so long in recognizing the nature of albinism. Throughout the nineteenth century it was regarded as a disease acquired in humid and insalubrious regions (from which such individuals often came) or produced *in utero* by psychic shock to the mother. Such ideas remind us that the simple concepts of heredity were not always a part of common sense. Those writers before Garrod, and Pearson *et al*, who attributed albinism to a defect in the parental germ were the reverse of scientific and espoused ideas which Pearson called "metaphysical or metaphysiological." Ascoles (1871) had recorded from Sicily for other reasons data about 24 families, 5 consanguineous, containing in all 60 albinos. There were two instances of direct transmission of albinism from parent to child. On this slender evidence Garrod rested his contention of recessive inheritance of albinism.

Mendelian vs. Ancestrian: Several apt studies published shortly after Garrod's Croonian Lecture should have left little doubt about the hereditary nature of albinism. Bateson was convinced of its hereditary transmission as a recessive trait by the available fraternities which totaled 197 normals and 126 albinos, plus the high incidence of consanguinity found (Church, 1909, p. 28). The pedigrees known included that of Fig. 2, which is reproduced in the original form with shaded symbols for the normally pigmented Negroes. The normally pigmented son of an albino had in two marriages to normal women a total of fifteen offspring, four of them albinos (Mudge, p. 122 in Church, 1909). It was criticized because of the small chance that two successive marriages to heterozygotes could occur. The incidence of heterozygotes was then supposed to be about twice the incidence of albinism! Thirty-one pedigrees of recessive albinism were reported by Davenport & Davenport (1910, 1916), including three unique marriages of albino to albino, each of which resulted in one or two albino children and no normally pigmented children. This report was described by Pearson *et al*, (Part IV, Biblo No. 667) as "An attempt to demonstrate that albinism in man is a "unit character" and obeys Mendelian laws," and "his data are sparse, and his investigation from the statistical, ophthalmological and microscopical standpoints very inadequate" (Part II, p. 490). Pearson was almost able to have judgement suspended on the hereditary nature of albinism in man until he should make known the outcome of the massive project he had undertaken for the study of this disease. The nature of this work and its time in history require special comment.

"A Monograph on Albinism in Man" was published in six quarto volumes in 1911

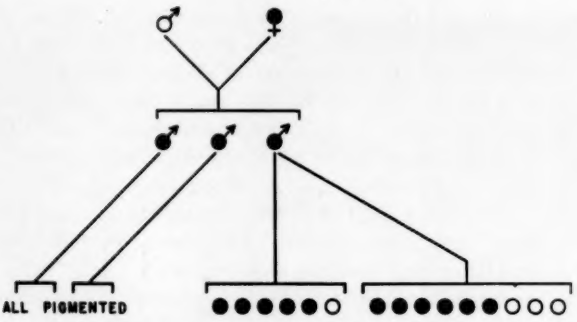

FIG. 2. Farabee's early pedigree of albinism, cited by Mudge (1909). Since the incidence of heterozygotes was then assumed to be about one hundredth the probable incidence, only convinced Mendelians found support for recessive transmission in this pedigree.

and 1913 by Pearson, Nettleship and Usher. Pearson was the director of the Francis Galton Eugenics Laboratory and of the Biometric Laboratory, and Professor of Applied Mathematics at University College, London. He initiated the project, and later induced the two physicians interested in the subject because of their ophthalmological studies to join him in its execution. This was the time of testing of Mendelism, and with the rumblings from the battles on evolution still audible, those who were not for Mendelism were judged to be against it.

Pearson's own words (November, 1908) made clear his position: "There is no definite proof of Mendelism applying to any living form at present" (Church, 1909, p. 155). His major effort was to apply exact methods to vital statistics, because "in nine cases out of ten Mendelians had not an elementary knowledge of how to deal with numbers, yet that knowledge was fundamental even to demonstrate Mendelism" (ibid., p. 131). He had denied that coat-color in horses or eye-color of man followed Mendelian principles, and the first demonstrations that they did were coupled with ironic comments on the fledgling science of statistics: "Professor Pearson has assured us that Biometry is destined to convert Biology into an exact science and to effect the salvation of biologists from the alleged perdition of theory, hypothesis, ramdom speculation, and vague terminology into which they had drifted before the biometrical angel had outspread her wings and come to earth to guard them and to lead their erring footsteps along a better road" (Mudge, p. 126, in Church, 1909). There was a reasonable suspicion that Pearson's biometry veiled an attempt to perpetuate Galton's hypothesis of heredity acting through continuous and fluctuating variations instead of the discontinuous variations called mutations: "every example of a mutation which occurs in Nature is a brick in the edifice of Mendelism and is a clod of earth dug out of the grave that is preparing for the Biometrician" (Mudge, p. 115 in Church, 1909).

The monograph on albinism appears to represent either the grave of some erroneous ideas, or laudable work killed by bad planning and naive biology. The wealth of material compiled on complete and incomplete albinism, on the various spotted conditions called "partial albinism", and on acquired leucoderma is at first over-

whelming. All known references, pedigrees and pictures bolstered by commissioned photographs, are reproduced in atlas volumes designed to accompany each of the three volumes of text. But the insistence that all biological phenomena involving color are related warns the reader. The orderly presentation of the history, geographical distribution, and varieties begun in Part I (1911) breaks down in Part II (1913). The detailed examinations of the structure of skin, eye, and hair in man is crowded by a welter of detail on animal albinism. Disjointed appendices by the authors and "distinguished specialists" appear on such subjects as the history and breeding of light colored Pekinese dogs, a report on the penis and scrotum of a South African Native with white glans penis, and the observations on the color of Norwegian Variable Hares throughout the seasons. The text of Part IV (1913) contains the individual case reports of all individuals shown in the pedigrees of the Part IV atlas volume. There are 654 numbered pedigrees, plus A to Z and AA to DD in extra plates (total 684), as well as pedigrees of the Pekinese spaniels. The preface to Part II says: "Part III. involving a general account of previous work on albinism in animals, a discussion of the vital statistics of albinism in man, and of the relation of albinism to other pathological states as well as the final reduction of our statistics of heredity of albinism in man will we hope to be ready towards the end of this year." Part III has never appeared.

The final two pages of text in the monograph, ones concluding a report on the muzzle and nose indices of albino dogs that was undoubtedly written by Pearson, must be taken as the summary of the monograph. After reiterating that the diversity of albinotic types (hereditary and acquired!) cannot be fitted into simple Mendelian theory, a conclusion of a sort is reached: "As we have seen in the course of this work albinism is a graded character, and we have every reason to believe that both in man and dogs separate grades are hereditary. Further than this we should hesitate to go at the present stage of our experimental work. Mendelism is at present the mode—no other conception of heredity can even obtain a hearing. Yet one of the present writers at least believes that a reaction must shortly set in, and that the views of Galton will again come by their own" (p. 490, Part III).

Recessive Inheritance: Citations which ascribe conclusions about the mode of inheritance of albinism to Pearson *et al*, are misleading. The apparent recessivity of complete albinism and the dominance of white spotting are in one place played off against one another to the discredit of Mendelism. The "monograph" remains a fascinating collection of items, a source book for works still unwritten on several different pigment diseases and phenomena. But the conclusions of the work were drawn eighteen years later by Hogben (1931). After a critical sifting of the pedigrees and statistical treatment of that data, he found 29 per cent of complete albino sibs in affected families. This fraction was somewhat above the expectation of 25 per cent for an autosomal recessive condition, perhaps only because the ascertainment had favored those families with unusually high proportions of albinos. The incidence of consanguinity in this and other studies ranged between 20 and 50 per cent. The earlier conclusions of Davenport and others that albinism was a recessive hereditary condition do not lessen the importance of Hogben's study. The value of the adequate statistical treatment of data as championed by Pearson can be shown in the

comparison of Hogben's conclusions with those of Magnus (1922). The latter found a total of 174 albinos in Norway, making an incidence of 1 per 10,000. Fifty families, 21 of them consanguineous, contained 108 of the albinos and 181 normal sibs. Lacking statistical methods he was forced to a descriptive analysis of individual families, and to a conclusion that albinism was both recessive and dominant in different families.

Subsequent studies have confirmed that complete albinism fits a recessive mode of inheritance quite precisely. After correction, the number of affected sibs in unselected families closely approaches 25 per cent (Sanders, 1938). A number of identical twins with perfect concordance in affected families have been reported (Wakefield & Dellinger, 1936; McCrackin, 1937; Hanhart, 1953). A number of concordant and discordant twins had been cited by Garrod. The possibility that heterozygotes can be detected clinically and that complete albinism is "incompletely recessive" (Waardenburg, 1947) has not yet been generally accepted. In some families a peculiar translucence of the iris on transillumination, independent of the degree of pigmentation, has been seen in the heterozygotes. Such studies are to be welcomed as possibly providing some indication of the number of different genes which may produce albinism in a recessive manner (Hanhart, 1953).

Alleles and Loci: There is a real possibility that complete albinism, though its transmission is uniformly recessive, can be produced by a series of allelic as well as non-allelic genes. The most impressive indication of different alleles is the report of two normally pigmented infants with good vision born from the union of two complete albinos (Trevor-Roper, 1952). The variations met in the degree of residual pigmentation, as well as the quality of color present in rufous and xanthous albinos, suggest the existence of multiple genes for albinism like those known to occur in guinea pigs (Wright, 1942). The invariable association of other abnormalities or characters with albinism in certain families, if this could be demonstrated, would provide another indication of a variety of genetic types of albinism. A different biochemical exploration might then be required for each. But until such a time, or until an extra biochemical explanation is in hand, complete albinism must be dealt with as a single entity.

III. PIGMENT PHYSIOLOGY

The casual reader may ask, "Are the pigment cells in albinism absent or just unable to make pigment?" It is obvious that colored materials of the body should early attract investigators, but it is unexpected that such a question could not be answered until now. In 1940, Meirowsky, who had been an active investigator of the melanotic pigment of the skin since the turn of the century, published "A Critical Review of Pigment Research in the Last Hundred Years." He attempted to list "what results can be looked upon as secured and from what points future research must be restarted." He considered largely elementary questions such as the identity of the cells forming pigment, the movement of pigment in the tissues and the general nature of its biochemical formation. These items are essential for the precise definition of the defect in albinism. Six of his nine fundamental questions would today be answered differently. There is still a need for ascertaining the correctness of our general con-

clusions, especially those based on textbook statements originating long before 1940. Only secondarily should we explore the specialized detail of this fascinating field. At the risk of being doctrinaire, some decision has been taken here on the correctness, or at least the relevance to albinism of the more popular aspects of pigment research. This is safer to do for the present subject than is often the case, since many different aspects of the pigment cell problem have been competently reviewed, and the reader can readily inform himself about doubtful points. Five excellent sources of information are Lorincz' review in Rothman's (1954) "Physiology and Biochemistry of the Skin", the published conferences on "Pigment Cell Growth" (Gordon, 1953) and "The Biology of Melanomas" (Gordon *et al*, 1948), and the reviews by Lerner and Fitzpatrick (1950, 1953).

Physical and Chemical Nature of Melanin: The primary concern in the study of albinism is the presence or absence of granules of brownish black pigment. Some explanation is therefore required for the variety of shades and tints of color normally seen in the body. Ignoring for the moment the yellowness of fat, the redness of blood, and other pigments which are not lacking in albinos (indeed these tints shining through the albino tissues give him his peculiar spectral quality), there remain a great variety of color effects referable solely to the sombre particles of melanin in a tissue. These are colors arising from physical structure and not from pigmentation *per se*. A single mechanism which gives rise by light scattering to the blue of the eyes or the blueness of deeply inbedded skin pigments, both called Tyndall blues after the discoverer of this phenomenon, will explain much of what is seen in normally pigmented individuals and what is missing in albinos.

Blue-scattering of light is of wide occurrence in nature, and accounts for the blue of the sky as well as of eyes. When light strikes microscopically divided, unordered particles greater than 1 μ in diameter, all wavelengths are reflected, and the material appears white. Much of the chalky character of the albino's skin is produced by a rather inefficient reflection of this type from the various cytological structures. There is superimposed on this a suffused pink from the hemoglobin showing through the translucent tissues. If particles are present less than 0.7 μ in diameter (and the melanin granules are smaller than this) only the short, blue light rays are reflected and the object appears blue. The longer redder rays pass through and are usually lost. If viewed by transmitted light such an object appears red (or yellow or brown), since only these longer rays come through. An iris with insufficient pigment to give it a hazel or brown color will show to the external observer only the Tyndall blue of the selectively reflected short rays of light, provided that the red light passing on through is absorbed and not reflected from the fundus. In the same way, a vein or a pigment deposit deep in the skin of a fair person will absorb the penetrating red rays and take on a bluish cast from the short rays reflected by the melanin granules in the skin overlying the object. The biological colors produced by this and related physical means, such as light interference, acting on the number, size and depth of successive layers of reflecting particles of pigment, are described in fascinating detail by Fox (1953). Since the breath-taking color displays of the perineum of certain baboons (male drill) and of the neck of turkey gobblers, for example, are produced simply by the arrangement of dark pigment particles, it is at least possible that a

variety of subtle tints in the eyes, skin and hair of man would disappear in the absence of similar undistinguished dark granules.

The color of normal skin has been attributed to five primary pigments on the basis of spectrophotometric reflectance measurements by Edwards and Duntley (1939) and the effects of these pigments are modified by the physical distribution patterns as discussed above. The pigments were oxy- and reduced hemoglobin, carotene, melanin and melanoid. Only the last two are missing from albinos. They were distinguished by their slightly differing general absorption of light in the violet end of the spectrum. The separate existence of melanoid as a pigment is uncertain, since it may only be melanin in the process of being cast off in the cornified skin. It is said to be formed independently of melanin, however, in the skin of eunuchs given testosterone (Edwards, Hamilton, Duntley & Hubert, 1941). The most convincing evidence from these studies that albinism might be considered purely as the absence of the single pigment, melanin (and its possible derivative, melanoid), is that no qualitative pigmentary differences were demonstrated between people of the same or different racial types. The clearly evident differences in skin color of people depended chiefly on the quantitative differences in the amounts of melanin present. These general conclusions have been confirmed by similar studies of others (Goldzieher *et al*, 1951).

At this point it is necessary to state that the term "melanin" still has no precise definition. It is merely the "dark pigment" localized in certain cells with its maximum absorption in the ultraviolet region. The modern usage which extends this histological definition to cover the brown or black polymers derived from the oxidation of tyrosine or dihydroxyphenyl compounds is based on an assumption which will be evaluated in due course. For the moment the soundest procedure will be to consider it purely as a cytological substance.

Melanin is seen in brown or black granules, usually located intracellularly. It reduces silver and gold salts and osmium tetroxide, which are often used to intensify its color, and it can be bleached to a light tan by strong oxidizing agents such as hydrogen peroxide or potassium permanganate. The melanin granules are specific structures which have been isolated by differential centrifugation of homogenized colored human skin, beef eyes and mouse melanomas (Mason, Kahler, MacCardle & Dalton, 1947). Electron microscopy of these preparations revealed the granules to be about 0.3 μ in diameter, and to have a uniform rounded or short rod shape more or less characteristic for each of these sources. These particles from the mouse melanoma are in chemical combination with at least one protein, a pseudoglobulin with specific antigenic properties, which can be progressively digested off by pancreatin to leave an increasingly high content of sulfur-amino acid bound to the pigment (Greenstein *et al*, 1940). This presumably indicates the means of binding of the pigment to the protein. More recently it has been unequivocally demonstrated that the pigmented particles from the mouse melanoma are analogous to the mitochondria of other cells. They consist of an elaborate array of chemical and enzymic constituents in addition to the pigment (Woods *et al*, 1950).

The identification of the pigment granules of the mouse melanoma cells as pigmented mitochondria is of great importance for the interpretation of studies of the

chemical composition of "melanin." Until it is obtained as a less complex chemical combination, it can be assumed that all samples of natural "melanin" represent part of the structure of the cell and not a simple chemical substance. The chemical analyses which have been reported, usually of material that had been extracted in alkali and precipitated with acid and that was still conjugated with protein, therefore, should not be expected to shed much light on the chemical nature of melanin. Indeed, almost nothing is known of the chemical nature of natural melanins.

It is a likely assumption that melanins are irregular polymers of benzenoid units, but it has not yet been possible chemically to degrade any naturally occurring melanins to some identifiable fragments which would identify the monomeric units of the polymer. The elaborate chemical work on the structure of melanins, reviewed authoritatively by Mason (1953), has been based exclusively on artifactual pigments produced *in vitro* by chemical or enzymic oxidation of phenols. One of the best known of these is the melanin formed by tyrosinase oxidation of 3,4-dihydroxyphenylalanine (dopa), for which it is virtually certain that the polymerizing unit is indole-5,6-dihydroxyquinone. Certain restrictions are known to limit to about three the variety of structures that may occur within the polymer. However, seventeen other naturally occurring phenolic substances which can be oxidized to melanins were listed in the above review. This could give "many different kinds of natural melanins, and this variety may be multiplied by the kinds of large molecules to which melanins are naturally attached and by the different modes of polymerization and conjugation possible, as well as by the different states of oxidation reductions of which melanins are capable. The structures of these naturally occurring substances, which have not been investigated from this point of view may then be quite different from anything already proposed." (Mason, 1953). Fig. 3 gives the structure of some known intermediates in the *in vitro* formation of dopa melanin, and one of the possible repeating units within this artificial melanin. In view of the above discussion these structures should only be considered to illustrate a general phenomenon, since they bear no necessary relation to the formation or structure of natural melanin in the tissues. Not only is the general structure of natural melanin in doubt, but so is the identity of the precursor from which it is formed.

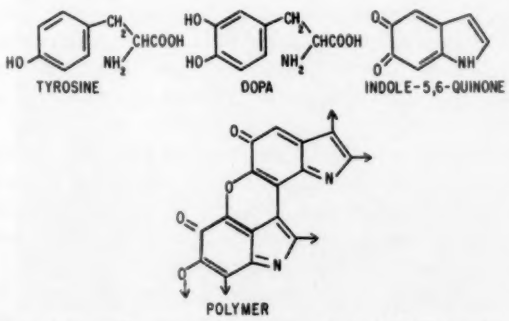

FIG. 3. Intermediates in the formation of dopa melanin *in vitro*. The polymer shown is one of several possible types (from Mason, 1953).

Embryology and Histology of the Pigment Cell: One of the two signal advances in pigment research in recent years has been the proof that there are specialized mammalian pigment cells distributed throughout the integument which arise from the neural crest (Rawles, 1948). The bulk of melanin pigment is located in dendritic melanocytes arrayed among and just below the basal cells of the epidermis and in the hair bulbs. Other pigment is transferred into the growing hair shaft. There are also melanocytes and melanin in the oral mucosa, pia mater and certain other surface membranes. Although pigment particles are found in other structures in lower animals, and even in man altered particles can be found in the keratinized layer of skin, deeper in the derma and in local lymph nodes, the source in man can be accepted as the melanocyte. This specialized cell does not arise autonomously in the surface membranes but migrates there under the control of unknown orienting factors from the neural crest at an early period in embryological differentiation. Statements that the pigment cell is a "nerve" cell in origin are deceptive, since the neural crest is merely tissue *beside* the neural tube proper.

The evidence for the origin of the cells does not depend upon uncertain cytological criteria for recognizing early, unpigmented or melanoblast stages of an elusive, migratory cell. By transplantation of mouse embryo fragments into the coelomic cavity of the chick embryo where development continued, it was shown by a variety of experiments that pigment developed only in those fragments containing neural crest or its migratory cells, and that fragments from which such cells were excluded would develop structurally normal skin and hair that was entirely pigment free (Rawles, 1953). Absence of melanocytes is therefore one possible cause for albinism. Failure of the cells to reach their proper destinations is a very reasonable explanation for the symmetrical patterns of depigmentation. Localized exclusion or destruction of melanocytes may explain certain types of piebaldness, as it has explained the colorless hair growing from an area of regenerated epidermis after freezing or irradiation injury (Taylor, 1949).

The melanocyte is a branched, light colored, "clear cell," staining less intensely than the surrounding basal cells, and from these it can also be differentiated by the lack of tonofibrillae and intercellular bridges. These criteria are hardly adequate for its identification in albino skin. Only when it contains melanin is it readily distinguished. Only pre-existing melanin can be darkened by silver impregnation. The dopa reaction gives gray to black staining even of the unpigmented dendritic cells when they are active, as they are immediately preceding as well as during actual melanin formation and after exposure of the skin to irradiation of various sorts. Since the dopa reaction may recede after pigment has been formed, it is possible to find cells which contain many melanin granules that give only a weak dopa reaction, and strong reactions in cells which have not yet accumulated pigment. Since dopa can also be oxidized non-specifically, especially by real or pseudo-peroxidases plus traces of peroxide, many non-melanocytes can give this reaction under certain conditions. The usefulness of the dopa reaction as a stain for the pigment forming melanocytes has been bolstered by the indisputable fact that albino skin does not give the reaction. This is of no value to the present question. Neither the silver stain which depends on the presence of pre-formed melanin, nor the dopa reaction which corre-

lates in a general way with the ability to form pigment, help us to decide if melanocytes (without pigment) are present in albinos.

Albino (Amelanotic) Melanocytes. Gold impregnation, introduced by Langerhans in 1868, has the happy facility of blackening both melanocytes and the very similar non-pigmented cells which can be found in equal numbers in albino skin. These are illustrated in Fig. 4. Some unknown property of the cell, perhaps connected with but surviving independently of its pigment forming ability, distinguishes by reaction with gold the colorless melanocyte from its surrounding colorless epidermal cells (Becker *et al*, 1952).

Further evidence for the existence of (amelanotic) melanocytes in the albino can be found in a second characteristic process of these cells, their occasional transformation into highly malignant melanomas. The literature often refers to the susceptibility of albinos to various forms of skin cancer, which is not unlikely in view of their lack of any pigmentary protection from sun light. But until recently no one had found any melanomas among albinos (Shapiro, Keen, Cohen & Murray, 1953). The first recorded case of malignant melanoma in a complete universal albino has now been described (Young, 1957). No pigment was found throughout the body or in the primary and metastatic sites of the melanoma, and both silver and dopa stains were negative. Yet the characteristic architecture of the cell, the junctional activity and the pattern of growth of the lesions identified these cells with those usually bearing pigment in a normal individual. Such a pigment-less melanoma in an albino must be distinguished from the so-called amelanotic melanomas frequently encountered in normally pigmented individuals. These are rarely, if ever, devoid of pigment (Fitzpatrick & Lerner, 1954). They are rich in tyrosinase which can be demonstrated

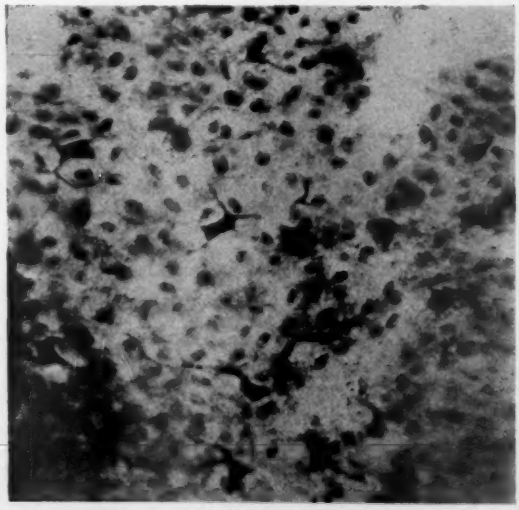

FIG. 4. Separated epidermis from albino with the melanocytes revealed by gold impregnation (from S. W. Becker, Jr., in Pigment Cell Growth, Academic Press, 1953).

simply by immersing them in tyrosine solution (Lerner & Fitzpatrick, 1953). Apparently the tumors are lightly pigmented because their growth has outstripped their tyrosine supply. In addition to this proof for melanocytes in albino man from the occurrence of a melanoma, there are hereditarily controlled melanomas that develop in the macromelanophores of certain fishes. These have also been produced in albino fish, where they appear as structurally typical tumors devoid of pigment (Gordon, 1948).

In summary, the direct visualization of melanocytes after gold impregnation and the occurrence of melanomas in albino tissues, plus the lack of evidence for any abnormality but depigmentation of the neural crest cell or its derivatives, implicate a sub-cellular defect in the melanocyte as responsible for the lack of pigment in albinism.

IV. BIOCHEMICAL MECHANISM OF MELANIN FORMATION

In view of the common assumption that tyrosinase and dopa produce melanin formation in human melanocytes, the reader should remember the absence of any real information about the chemical constitution and precursors of natural melanin. A further quotation from Mason (1953) puts the assumption in perspective: "The identities of propigments have had to be *deduced* from diphenols *coexisting with* or probably produced in the presence of phenol oxidases, or from the experimentally determinable *specificities* of these phenol oxidases. It is on such grounds that 3,4-dihydroxyphenylalanine is widely considered to be the propigment in mammalian melanocytes." On the two facts italicized above, the occurrence of a diphenol in the skin and the specificity of the phenol oxidase found there, rests whatever inferences have been drawn about the biochemical mechanism of pigment formation in mammals.

A single fact, that something was present in the pigment cells which made pigment out of a diphenol, was the basis of all thought about mammalian melanin formation. Recently a second fact has been learned. The two known facts support the commonly accepted views, but they are slender evidence supporting a colossus of theory. The first known fact was the presence in pigment cells of something like an enzyme. Specifically, this was the "dopa oxidase" reaction discovered by Bloch with the use of 3,4-dihydroxyphenylalanine added to frozen skin slices (Bloch, 1927). Melanocytes were blackened by this reaction. The much more elaborate information available about pigment formation in plants and insects, whose extracts contained an active tyrosinase that oxidized tyrosine to dopa and on to melanin, lent strength by analogy to this isolated fact known about pigmentation in mammals. The general acceptance of a similar scheme for the pigment formation in higher animals required more detailed chemical evidence that was slow in coming. Dopa, for example, was known to occur physiologically only in beans.

The original choice of dopa as a reagent developed from certain valueless clinical considerations of the pigmentation found in Addison's disease (adrenal hypofunction) and from the excretion of catechol-like compounds by patients with melanomas. These considerations directed Bloch's attention to epinephrine and catechol as possible pigment precursors. Only the chemically related dopa formed pigment in skin slices. This pragmatic basis, without evidence for the natural occurrence of dopa at the site of mammalian pigment formation or for the presence of the dopa unit in

natural melanin, was the sole reason for the provisional identification of dopa as a pigment precursor in animals.

The relevance of Bloch's work to the pigmentation problem therefore stood on what evidence there was for a specific phenol oxidase in skin which formed pigment from dopa. The histochemical usefulness of the "dopa reaction" was amply confirmed, but the existence of this "dopa oxidase" was hotly contested. Meirowsky (1940) was convinced only that a non-specific catalyst, probably not an enzyme, was present in both pigment-forming and other cells. His review gives the cogent arguments against Bloch's interpretation of the dopa reaction. Now that additional evidence supports Bloch's observations, it is of interest to see what kind of evidence for a specific enzyme was produced by (Bloch's) early use of cytochemistry. The technique consisted of immersing frozen sections of skin into a dilute solution of dopa buffered at physiological pH and noting the melanin deposition which occurred after 24 hours at room temperature. The deposition of melanin was the most intense in the regions such as the basal layer of epidermis and hair follicles, it was localized predominantly in the specialized cells he called melanoblasts (melanocytes), and it did not occur in albino skin or skin affected with the localized loss of pigment called vitiligo. He concluded that this dopa reaction was a reliable indicator of the active capacity of cells to form pigment. On this empirical observation there was general agreement provided that the slight degree of generalized darkening of the slice was ignored which resulted from the non-specific oxidation of dopa. Few of the antagonists ignored this background staining, however.

The evidence that the dopa reaction was due to an enzyme, dopa oxidase, was highly suggestive. The dopa reaction occurred only at a neutral pH range, it was suppressed by heating the slice to 100° C or otherwise denaturing the proteins, and it was inhibited by dilute solutions of hydrogen sulfide or cyanide. To these enzyme-like properties was added the unique specificity. The reaction occurred only with the natural L-isomer of dopa. Except for the background color produced by all of the easily oxidized diphenols, melanin was not formed from a large number of phenols and related compounds including tyrosine, tryptophan and the unnatural D-isomer of dopa. To this cytochemical evidence, Bloch and Schaaf (1925) added the demonstration that a similar reaction was catalyzed by extracts of new-born rabbit skin from pigmented but not from albino animals.

The inadequacies of the above explanation of the mechanism of melanogenesis are briefly enumerated, without resort to the polemical exceptions that have been taken to each item of evidence. Probably dopa was converted by enzymic catalysis to an insoluble pigment in the melanocytes of man, and this reaction was possibly absent in the albino skin. But the darkening of certain areas in skin slices or extracts caused by a substance which also darkened spontaneously in watery solution was not sure evidence for a physiological process. The specificity of the reaction for dopa hinted at an enzyme, but this fact lost weight without evidence that dopa occurred in the skin. Tyrosine was a more reasonable precursor and was supported by the analogy with the tyrosinase reactions in lower forms of life, but tyrosine was unable to act as a pigment former in mammalian skin. Against the clear cut correlation of a positive dopa reaction occurring where there was pigment formation, particularly in the

comparison of normal and albino skins, could be set a bewildering number failures of this correlation. The dopa reaction did not parallel the quantitative changes in pigmentation seen in normal skin, and this problem remains to be explained, perhaps in terms of the activation and regulation of the pigment forming enzyme *in vivo*. There was no general acceptance of the Bloch scheme of melogenesis because of (1) the inability to establish any chemical similarity between natural melanin and that formed in the dopa reaction, (2) the absence of chemical evidence for a dopa oxidase to support the cytochemical evidence, and the (3) the failure to prove the physiological occurrence of dopa as a potential pigment precursor. There is now additional evidence on the last two points.

Mammalian Tyrosinase: The second of the two major advances in pigment cell research in recent years has been the demonstration that melanin is formed enzymically from tyrosine in mammalian skin. The over-all reaction resembles that long known to occur in lower forms of life (Raper, 1928) and the reactions, passing through dopa as an intermediate, encompass and so support the observations made by Bloch. The mammalian tyrosinase was first demonstrated unequivocally by Hogeboom and Adams (1942) in extracts of the Harding-Passey mouse melanoma. There had been earlier studies on horse melanomas that were less convincing. The tumor extracts had sufficient activity for the reaction to be followed by oxygen consumption and to permit other biochemical manipulations which left no doubt about the enzymic nature of the reaction. Only tyrosine or its ethyl ester were substrates. Purification of the enzyme beyond a certain stage was not possible, however, because it was part of the same mitochondrial unit identified with the melanin granule (Woods *et al*, 1950). Like the soluble enzymes of lower forms, the melanoma enzyme also required copper. Dopa was recognized as an essential intermediate in the reaction, being formed from tyrosine and further oxidized to melanin. Dopa acted also as a necessary cofactor for the initial oxidation of tyrosine (Lerner *et al*, 1949). It remained only to confirm these observations on melanomas with studies on the much smaller amounts of tyrosinase available in normal skin.

By the same procedures used by Bloch and incubating white human skin slices with tyrosine instead of dopa, melanin was formed in the melanocytes (Fitzpatrick *et al*, 1950). An essential difference from the earlier work was that the skin was irradiated with ultraviolet light some days before its removal in order to activate the tyrosinase. In the skin of young mice (Foster & Brown, 1957) and of guinea pig fetuses (Foster, 1956) the tyrosinase (here largely restricted to the hair bulbs) was fully active without irradiation if endogenous inhibition was overcome by iodoacetamide. Presumably the enzyme can be demonstrated only after overcoming the sulfhydryl inhibition first demonstrated by Rothman *et al* (1946). In minced skin preparations the tyrosinase activity was demonstrated to share all of the properties of the tyrosinase from melanoma (Foster & Brown, 1957). It specifically oxidized L-tyrosine to dopa and dopa to melanin, it was measured by oxygen uptake as well as by melanin formation, and it was inhibited by copper chelating reagents. In the albino mouse there was no such reaction. More complicated results were obtained with some of the allelic series at the albino locus (C) in the guinea pig, but it is premature to expect an explanation for all of the great variety of albinotic conditions in animals with this single qualitative test.

V. THE ALBINO DEFECT

The reaction of an enzyme in the mitochondria of melanocytes which normally forms melanin and conjugates it to these granules is missing in at least some albino men and animals. The melanocytes themselves are apparently present and normal except for their pigment lack. Experiments do not appear to have been done to decide whether the granules normally containing both the pigment and the enzyme are themselves missing from the melanocytes of the albino, or whether they are present but incomplete. Since these particles have many other enzyme activities, they could be readily identified. Since these other activities include the major respiratory systems of the cell, it is unlikely that the particles are missing. Even if they are shown to be present, a variety of abnormalities of these particles could still account for the inability to form pigment, and one of these possibilities is the absence or defectiveness of the tyrosinase. The elucidation of this problem will come from the biochemical analysis of the pigment forming systems in the variety of genetic strains of animals with different coat colors (Russell, Russell & Brauch, 1948). The number of such different strains, even more than the indications for genetic heterogeneity among human albinos, means that a lesion at any of several biochemical sites can cause albinism. The small number of known chemical reactions in pigment formation does not mean that the great variety of loci controlling coat color must act at these few biochemical loci. Only the bare outlines of the biochemical reactions in pigment formation have been perceived, and to this must be added the complexities of regulation. There are signs that the fifty years of complacence with an adequate theory and inadequate physiological facts about albinism is ending.

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Birth Order, Parental Ages, and Sex of Offspring

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INTRODUCTION

VARIATIONS IN THE PROPORTION OF MALE BIRTHS (i.e., the secondary sex ratio) have been analyzed many times as a function of those characteristics of the parents, the sibship, or the environment, for which available data lend themselves to statistical treatment. Among the interesting relationships discovered previously is the observation that the age of the mother apparently has no, or very little, effect on these changes whereas the increasing age of the father is correlated with a decreasing secondary sex ratio (Novitski, 1953). This is a most puzzling result since one can readily imagine a number of ways in which some factor related to maternal age might be responsible, as, for instance, differential mortality of the two sexes before birth, whereas a system related to the age of the father (and relatively independent of the mother's age) is not so easily conceived.

An attempt to assess the relative contributions of the parental ages and birth order showed that there was no simple unifying interpretation of data that gave, on the one hand, the parental ages and sex ratio of offspring and, on the other hand, the maternal age, birth order, and sex ratio (Novitski and Sandler, 1956). It was therefore suggested that a more informative interpretation would depend on the analysis of data that gave, for each birth, the sex of the child, both of the parental ages, and the birth order simultaneously. Through the kindness of Dr. Halbert Dunn and his associate, Dr. Delbert Waggoner, of the National Office of Vital Statistics, such data for the year 1955 were made available to us, and this paper is concerned with the analysis of those data.

METHODS AND RESULTS

This analysis differs from the previous one in several important respects. Because live births for the year 1955 were classified simultaneously according to three criteria—age of father, age of mother, and birth order—it was possible to fit a regression function of sex ratio on all three variables simultaneously. Furthermore, the ORACLE, a high-speed digital computer operated by the Mathematics Panel at Oak Ridge National Laboratory, was available for use in the analysis. As a result we were able to fit a quadratic regression surface to the data (the existence of nonlinear effects had been suggested earlier) and to make several subsidiary calculations that would have required a prohibitive amount of work with desk calculators. In fact, it would have been possible to fit a cubic or higher order regression to the data with almost equal facility, but the data were not considered precise enough for this

Received January 4, 1958.

* Operated by Union Carbide Nuclear Company for the U. S. Atomic Energy Commission.

purpose. The fitted equation can be viewed as a Taylor's series approximation to the true regression function provided that the function admits a convergent infinite series expansion.

The following notation will be used:

x_1 = age of father, coded as in table 1
x_2 = age of mother, coded as in table 1
x_3 = birth order minus one
N_c = number of births in a given cell of table 1
N = total number of births
M_c = number of male births in a given cell
M = total number of male births
y = observed sex ratio in a given cell = M_c/N_c
Y = regression estimate of sex ratio for any x_1, x_2, x_3.

Since the N_c vary considerably in table 1, each y must be assigned an appropriate weight (w) and the regression function estimated by minimizing $\sum w(y - Y)^2$. The variance of y is estimated by $y(1 - y)/N_c$, assuming binomial errors, and ordinarily one would use the reciprocal of this quantity as the weight. However, only negligible errors are introduced if we take $w = N_c/\bar{y}(1 - \bar{y})$, where $\bar{y} = M/N$, because the true sex ratio in any cell in table 1 will differ only slightly from $\bar{y}$.

As a first step in the analysis, the function,

$$Y = b_0 + b_1x_1 + b_2x_2 + b_3x_3 + b_{11}x_1^2 + b_{22}x_2^2 + b_{33}x_3^2 + b_{12}x_1x_2 + b_{13}x_1x_3 + b_{23}x_2x_3,$$

was fitted to the 175 observed sex ratios given in table 1 by the weighted least-squares procedure indicated. The estimated coefficients and their standard errors are shown in table 2; the residual sum of squares is 218.95 with 165 degrees of freedom. Under the null hypothesis that $E(y) = Y$, the residual sum of squares is distributed approximately as χ^2 and corresponds to a significance probability of 0.003. The value of χ^2/d.f. agrees well with the values obtained in analyses referred to above, although the significance level is different because of the greater number of degrees of freedom. Several interpretations of the significant χ^2 are possible. It is well known that the use of weights based on observed data introduces a bias into the computed χ^2. However, since all of the true sex ratios must differ only slightly from one half, this effect is negligible. A second possibility is that sampling errors include a component that is extrabinomial. As a check on this possibility, the 1955 data were compared with data from previous years for corresponding subclasses of the three independent variables. This analysis indicated a relatively uniform difference in sex ratio for most comparable subclasses (possibly because of the inclusion of nonwhite births in the 1955 data) but gave no evidence of extrabinomial variation. If these two possibilities are rejected, the natural conclusion would be that the departure of the computed χ^2 from its expectation is caused primarily by the failure of the quadratic model to explain all of the variation in sex ratio. A better fit might be obtained by including terms of higher order; alternatively, it is entirely possible that factors other than parental ages and birth order have some effect on sex ratio and that

TABLE 1. TOTAL LIVE BIRTHS AND SEX RATIO IN THE U.S.A. BY AGE OF FATHER, AGE OF MOTHER AND BIRTH ORDER: WHITE AND COLORED, 1955

(Source: National Office of Vital Statistics)

Age of father (yr)→				Under 20		20–24		25–29		30–34		35–39		40–44		45–49	
x_1→				0		1		2		3		4		5		6	
Age of mother (yr)	x_2	Birth order	x_3	No. of births N_e	Sex ratio y	No. of births N_e	Sex ratio y	No. of births N_e	Sex ratio y	No. of births N_e	Sex ratio y	No. of births N_e	Sex ratio y	No. of births N_e	Sex ratio y	No. of births N_e	Sex ratio y
		1	0	67,764	.519730	174,493	.516405	40,895	.517814	6,282	.496975	1,655	.502115	483	.476190	227	.590308
		2	1	11,563	.506270	65,066	.509467	19,103	.508088	3,382	.517150	943	.503712	309	.533981	144	.479167
Under	0	3	2	1,165	.509013	13,712	.514367	5,115	.498338	1,096	.535584	303	.511551	127	.456693	53	.547170
20		4	3	113	.486726	2,140	.495327	1,148	.515679	234	.517094	83	.469880	33	.545455	13	.461538
		5+	4	30	.700000	338	.565089	194	.520619	53	.509434	26	.461538	8	.375000	6	.333333
		1	0	7,830	.515837	226,762	.515571	167,747	.514346	31,579	.511289	6,811	.519601	2,021	.518060	647	.511592
		2	1	2,815	.502309	173,484	.512681	184,963	.510756	38,359	.510284	8,412	.519853	2,354	.505098	818	.512225
20–24	1	3	2	529	.466919	68,661	.510872	104,898	.513508	25,700	.515837	6,024	.508300	1,910	.526702	653	.509954
		4	3	139	.539568	20,546	.512362	44,556	.514072	13,300	.509098	3,361	.506397	1,175	.483404	435	.517241
		5+	4	52	.576923	7,273	.503919	23,102	.507965	9,274	.506038	2,698	.512231	945	.512169	395	.470886
		1	0	184	.478261	15,473	.515349	95,187	.514766	51,912	.510499	13,698	.513433	3,718	.490048	1,119	.528150
		2	1	79	.506329	14,019	.521435	158,439	.513819	105,729	.513227	24,820	.507977	5,956	.525353	1,750	.521143
25–29	2	3	2	54	.444444	7,857	.506427	121,294	.512663	102,507	.510424	24,763	.514598	5,951	.517728	1,745	.490545
		4	3	25	.520000	3,552	.513514	61,786	.512980	60,853	.511758	16,535	.508255	4,434	.509021	1,492	.508043
		5+	4	47	.297872	2,848	.514396	51,092	.499315	62,916	.511746	21,677	.513032	7,019	.507907	2,827	.506898
		1	0	12	.583333	880	.498864	10,339	.521134	29,494	.518241	16,928	.514828	6,206	.510313	2,011	.522626
		2	1	11	.454545	856	.511682	16,129	.520863	69,949	.515233	40,401	.512958	12,028	.512388	3,238	.507412
30–34	3	3	2	8	.625000	681	.516887	13,242	.507401	84,914	.516723	54,315	.517021	14,013	.512239	3,541	.505225
		4	3	6	.333333	459	.488017	8,088	.504080	57,010	.513156	40,820	.513547	11,075	.504199	2,928	.508538
		5+	4	25	.520000	737	.469471	9,157	.508900	67,265	.506727	64,623	.508890	23,672	.511617	7,655	.514958
		1	0	6	.666667	94	.478723	1,072	.524254	4,393	.504211	9,454	.510260	6,086	.519717	2,379	.518705
		2	1	3	.0	109	.522936	1,382	.520984	8,015	.504679	21,657	.517015	12,454	.505621	4,061	.503571
35–39	4	3	2	1	.0	80	.487500	1,252	.496006	8,385	.519141	31,662	.509570	18,538	.513809	4,958	.514320
		4	3	1	1.000000	66	.469697	859	.534342	6,108	.511297	26,899	.515595	17,174	.513916	4,645	.508504
		5+	4	10	.600000	162	.537037	1,582	.498104	8,508	.514104	49,011	.506907	44,387	.511749	15,697	.505319

TABLE 2. FITTED CONSTANTS AND STANDARD ERRORS FOR THE COMPLETE SECOND DEGREE REGRESSION EQUATION

Coefficient	Estimate	Standard error	t - ratio
b_i	$\hat{b}_i \times 10^3$	$s\hat{b}_i \times 10^3$	$t = \lvert \hat{b}_i \rvert / s\hat{b}_i$
b_0	515.620	1.1310	—
b_1	−0.5195	1.0474	0.496
b_2	0.5184	1.1100	0.467
b_3	−1.9029	0.8380	2.271
b_{11}	−0.2676	0.2513	1.065
b_{22}	0.0077	0.3893	0.020
b_{33}	−0.3208	0.2105	1.524
b_{12}	0.2031	0.4803	0.423
b_{13}	0.8016	0.2908	2.757
b_{23}	−0.3024	0.3516	0.860

these factors are not represented in our analysis. When appropriate data for additional years become available, further elucidation of the point may be possible.

Any regression analysis may be interpreted as a method for explaining the total variability in the data, as measured by the total sum of squares (weighted, if necessary), in terms of the factors by which the data are classified. When these factors can be quantitatively represented, it is customary and often useful to consider the functional relationship between the dependent variable (in our case, sex ratio) and the independent variables representing the factors being studied. Usually, the mathematical form of such relationships is unknown, and one ordinarily begins by assuming a simple linear or quadratic model such as the one described above. When this is done and the regression analysis is completed, it is possible to associate with each term or group of terms in the model a sum of squares which represents that portion of the total variability attributable to the particular term or group of terms being considered. Frequently, we refer to this sum of squares as a reduction (in total variability), since it reduces the amount of variability that is unexplained. The discussion that follows depends on arguments of this nature.

An examination of the t ratios in table 2, based on observed error variances, reveals clearly that certain terms in the regression contribute very little to the reduction in total sum of squares. Since the facilities of the automatic computer were available, we decided to examine the fits for several subsets of the ten fitted constants in an effort to determine the minimum number of terms in the regression equation that would be required to account for the variations in sex ratio. Without high-speed computing equipment, this type of analysis would probably not be feasible.

The results are shown in table 3. The total sum of squares ($\sum wy^2$) is 2640.86 and the reduction attributable to b_0 is 2350.92, which leaves a remainder of 289.94 to be reduced by fitting the other constants. Because every constant involving age of mother (x_2) had small t values in table 2, the first step was to eliminate this independent variable completely from the regression. From table 3 it can be seen that the additional reduction attributable to all terms involving x_2 is only 4.52, and an F test yields a significance level greater than 25 per cent. Thus, as was suggested by earlier work, the direct contribution of age of mother to the variations in sex ratio

TABLE 3. REDUCTIONS IN SUM OF SQUARES DUE TO REGRESSION

Constants fitted	Reduction attributable to constants fitted		Additional reduction attributable to remaining constants	
	Degrees of freedom	Sum of squares	Degrees of freedom	Sum of squares
$b_1, b_3, b_5, b_{11}, b_{33}, b_{55}, b_{13}, b_{15}, b_{35}$	9	70.99	0	0
$b_1, b_3, b_{11}, b_{33}, b_{13}$	5	66.47	4	4.52
$b_3, b_{11}, b_{33}, b_{13}$	4	66.46	5	4.53
b_1, b_3, b_{33}, b_{13}	4	64.73	5	6.26
b_1, b_3, b_{11}, b_{13}	4	61.78	5	9.21
b_3, b_{33}, b_{13}	3	58.70	6	12.29
b_3, b_{11}, b_{13}	3	61.70	6	9.29
b_1, b_3, b_{13}	3	60.38	6	10.61
b_3, b_{13}	2	56.98	7	14.01
b_5, b_{33}	2	54.17	7	16.82
b_3	1	53.63	8	17.36
b_{33}	1	51.77	8	19.22
b_{13}	1	31.23	8	39.76
b_5	1	5.84	8	65.15

is not significant. As a check on this result, chi-square heterogeneity tests were performed among maternal age classes within each of the 35 subclasses represented by combinations of the five birth orders and seven paternal age classes. The number of significant chi-squares found was no greater than one would expect from random binomial variation. This simple calculation provides additional evidence in support of the hypothesis that maternal age has no effect on sex ratio. It also strengthens the previous observation that extrabinomial variation, if present, must be relatively small, and it minimizes the likelihood that any appreciable heterogeneity has been introduced by pooling data for two races.

As the next step in the analysis, subsets of the five remaining constants were examined, and the corresponding additional reductions in sums of squares are shown in table 3. It is immediately apparent that b_1 contributes nothing significant to the regression since eliminating it leaves the reduction in sum of squares virtually unchanged. Consideration was then given to dropping individual constants from the subset (b_0, b_3, b_{11}, b_{33}, b_{13}), but from table 4 it can be seen that each of these constants contributes significantly to the regression. Nevertheless, the successive tests of significance are not independent, and there is some doubt as to whether the quadratic term for birth order should be retained and whether the quadratic term for father's age might be replaced by the linear term. These are borderline decisions, however, that depend primarily on one's interpretation of the P-values in analyses of this sort. In our judgment none of the constants shown in table 4 can be safely omitted from the regression.

The surface described by the final regression equation,

$$Y = b_0 + b_3x_3 + b_{11}x_1^2 + b_{33}x_3^2 + b_{13}x_1x_3 ,$$

can be examined in various ways. In figure 1, contours representing equal sex ratios have been plotted, and the fitted surface can be visualized quite readily. The varia-

TABLE 4. FITTED CONSTANTS AND STANDARD ERRORS FOR FINAL REGRESSION EQUATION

Coefficient	Estimate	Standard error	t - ratio	Significance level
b_i	$\hat{b}_i \times 10^3$	$s_{\hat{b}_i} \times 10^3$	$\lvert\hat{b}_i\rvert / s_{\hat{b}_i}$	P
b_0	515.0620	0.6384	—	—
b_3	−1.8478	0.7788	2.373	.025
b_{11}	−0.1892	0.0778	2.432	.021
b_{33}	−0.3825	0.2010	1.903	.062
b_{13}	0.6757	0.2212	3.055	.003

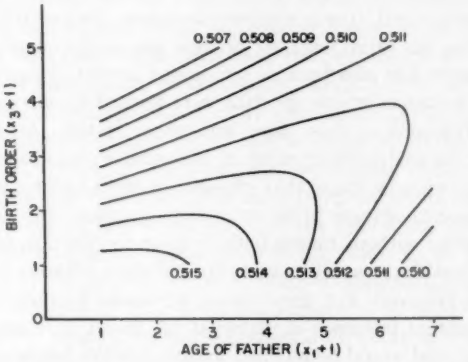

FIG. 1. Contours of equal sex-ratio plotted as a function of birth order and age of father, computed from final regression equation.

tions in Y as a function of either independent variable when the other is held constant can be obtained from figure 1 by examining appropriate cross sections of the surface. Thus, when Y is plotted as a function of x_3 for each value of x_1, (vertical cross sections) all curves are found to be convex downward; i.e., sex ratio seems to decrease more rapidly at higher birth orders, at least for young fathers. But for older fathers there seems to be very little dependence on birth order. In other words, sex ratio seems to depend primarily on birth order, decreasing as birth order increases, but this dependence diminishes rapidly as age of father increases, and accounts for the significance of the interaction term (b_{13}) in the regression equation. Alternatively, Y might be plotted as a function of x_1 for each value of x_3 (horizontal cross sections). This shows a negative regression of sex ratio on age of father for low births and just the opposite for high birth orders. Perhaps it should also be pointed out that by reference to figure 1, successive pairs of values for age of father and birth order can be chosen such that both variables increase but sex ratio remains unchanged. Previously there has been no evidence adduced that would have suggested such a relationship.

DISCUSSION

In assessing the reliability of these results, we must remember that the data used are for only one year, and include about four million births. Ordinarily this would

be considered a very large sample, but the magnitude of the effect being studied is only about one per cent and the observations are necessarily clustered along a diagonal in the x_1, x_2, x_3 space owing to the high correlations among these three variables. When more data of this type become available, the study will be continued. It is probable that future analyses will result in some changes in the relationships as they are now conceived, but it is most unlikely that the conclusions with respect to age of mother will be altered.

The apparent lack of any effect of the maternal age, either as a linear, quadratic, or interaction component with any of the other variables must be reemphasized. In the works previously cited, it was considered curious that maternal age showed no relation to changing sex ratio, not only because one might expect such an influence for biological reasons, but also because one might predict the appearance of a relationship in those instances where the data were limited to only parental ages, since the probable correlations of those ages with other factors (as, for instance, birth order) that might themselves have an effect on sex ratio should show up as a spurious relationship. Since we now know that changes in birth order and paternal age are both directly related to changes in the secondary sex ratio, it is clear that birth data must not be analyzed without taking both of these factors into account or, at least, that it is not advisable to analyze such limited data without being aware of the inevitable pitfalls involved. For this reason, we would hesitate to place any great reliance on an apparent influence of maternal age based on a simple breakdown by parental ages only, and would be inclined to question the relevance of such analyses to a biological interpretation of the causes of variations in sex ratio. Specifically, Lejeune and Turpin (1957a, 1957b) have analyzed data from the U. S. Public Health Service, giving the sex ratio of live births as a function of the parental ages for the period from 1946 to 1956.[1] They report that, although the effect of the paternal age is most pronounced, there is nevertheless a significant effect of the maternal age and that this might be interpreted as evidence for a higher incidence of sex-linked lethals in older women than in younger ones. It is our opinion that whereas the conclusion may be correct and, in fact, sounds plausible on genetic grounds, there is no evidence for it at the present time. It might be pointed out in this connection that the signs of the small, insignificant linear and quadratic regression coefficients on the age of the mother are in the wrong direction for an interpretation in terms of sex-linked lethals; that is, they are now positive, whereas those coefficients from analyses that do not take into account all three variables at the same time are negative.

Lest the intent of the preceding argument be misunderstood, it should be pointed out that we place no great reliance on birth order or paternal age as having a direct influence on secondary sex ratio but feel rather that these two items represent easily characterized attributes of any given birth, for which large amounts of data are available, and that they are, in all probability, themselves correlated with other

[1] The tabulations for the years 1951 to 1953 inclusive are based on a 50% sample. The totals given by Novitski and Sandler (1956) which include these years are therefore inaccurate. This inaccuracy does not substantially affect the general conclusions presented in that paper, but any worker wishing to use those totals should be aware that the estimates of error derived from those tables will be somewhat smaller than they should be.

factors more closely related to the true causes of the variations in sex ratio. It is therefore almost certain that there exist other attributes of a birth that, when known and properly available in statistical form and incorporated in an appropriate analysis, will show birth order, or parental age, or both, *as such* to be of no direct influence in altering the secondary sex ratio. The value of an analysis of the sort presented here rests in the demonstration that certain factors formerly considered important may represent spurious statistical correlations. Directing attention to the factors that seem to be most closely correlated with sex-ratio changes leads to the formulation of additional questions that may ultimately reveal the causes of those changes.

Little if anything can be said about the possible biological basis for the changes reported here. The basis for changes that have their expression as a function of the age of the male or of birth order, by themselves, would not be difficult to imagine, but one that depends on both of these factors simultaneously (as represented by the highly significant interaction term b_{13}) is not so easily conceived. There is some possibility, of course, that with the accumulation of more data, the relations will in some way be changed so that they seem more comprehensible in simple biological terms. It is also possible, as implied earlier, that the interaction term is simply a reflection of effects not adequately represented in the model or of the inadequacy of the functional form of the present model in terms of identifiable factors. Nevertheless, it would be a mistake at this stage to dismiss the interaction term as of no real significance purely because no simple biological explanation is at hand.

ACKNOWLEDGEMENT

We are grateful to Mr. G. J. Atta for assistance with the ORACLE computations and to Dr. E. R. Dempster for suggesting the chi-square homogeneity tests within birth order-paternal age subclasses.

SUMMARY

An analysis of U. S. birth data giving simultaneously the parental ages, birth order, and sex of offspring for the year 1955 shows that the variation in secondary sex ratio is independent of the mother's age but is dependent on both birth order and paternal age. It is further shown that the relationships are not linear and cannot be represented adequately without the inclusion of a component that reflects an interaction between birth order and age of father.

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On the Relationship of the Blood Group Antigens Mi^a and Vw to the MNSs System

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THE DISCOVERY, in 1927, of the MN system of blood groups was the brilliant achievement of Landsteiner and Levine. Subsequent work has entirely confirmed the original findings; it has also shown that the genes and antigens M and N are but part of a complex system. An account of the system as we now understand it will be found elsewhere (Race and Sanger, 1958). The present paper deals with two antigens, called Mi^a and Vw, which are part of the MNSs system but whose precise place in that system remains undecided. When their place is known then will be the time to search for more appropriate symbols.

The antigen Mi^a was discovered by Levine, Stock, Kuhmichel and Bronikovsky in 1951. Anti-Mi^a, the antibody which identified the antigen, was made by a mother in response to immunization by her Mi(a+) fetus which, as a result, had severe hemolytic disease. The antigen was shown to be inherited as a dominant character and it was evidently rare, for no example was found in testing 425 random people.

The antigen Vw was discovered by van der Hart, Bosman and van Loghem in 1954. The antibody, anti-Vw, was made by a mother in response to immunization by her fetus. The father had the antigen and so had several members of his family; it was not present in 740 blood samples from random Dutch people. The antigen was shown to be inherited as a dominant character. Sanger, studying the pedigree, noticed that the gene *Vw* was linked to the MNSs locus and was travelling with *Ns*. As there were 12 non-cross-overs and no cross-over it seemed likely that *Vw* was actually part of the MNSs system and that the linkage was of the very close type first recoginzed in Rh.

It was then found (Levine *et al.*, 1956) that those members of the Dutch family who were Vw+ were also Mi(a+), so it was naturally assumed that the antigens Mi^a and Vw were identical. But, in a preliminary communication, the present

Received April 20, 1958.

* Supported, in part, by a research grant, H-3437, from the National Heart Institute, Public Health Service.

authors (Wallace *et al.*, 1957) stated that the antigens were not identical: about half Mi(a+) people were Vw+ and about half were Vw−. Furthermore, in all the families studied at that time, in which the segregation was clear, the gene or genes responsible for the Mi(a+) Vw+ reaction were travelling on an *Ns* chromosome, while those responsible for the Mi(a+) Vw− reaction were travelling on an *MS* chromosome.

In the present paper we give details of these families and of others more recently tested, together with the results of tests on random white people.

The investigation began when, almost simultaneously, examples of anti-Mi^a were found in Buffalo and in Glasgow. In Buffalo the antibody was immune and had been the cause of hemolytic disease; the clinical and serological aspects of the case are being reported by Mohn, Lambert and Rosamilia (1958). In Glasgow two examples of anti-Mi^a were found, one in an anti-E serum and the other in an anti-D+C+E serum which unexpectedly reacted with a *cde/cde* member of the staff (in both the anti-Mi^a appeared to be 'naturally occurring' and in both it so happened that anti-Wr^a was also present).

FREQUENCIES

In order to get some idea of the frequency in whites of the two phenotypes, Mi(a+) Vw+, and Mi(a+) Vw−, the blood of nearly four thousand people in Glasgow and in London was tested with anti-Mi^a. The London samples were all tested with anti-Vw as well (the serum having been kindly provided by Dr. van Loghem). When Mi(a+) samples were encountered in Glasgow they were sent to London where they were further tested with anti-Vw. The results are shown in table 1. Large numbers of samples from whites and negroes have also been tested in Buffalo; these are yet to be analyzed and will be the subject of another paper.

None of the nine positive people of table 1 were known to be related to each other. Though the positives are few it seems that Mi(a+) people are more often Vw− than Vw+. It looks as if the incidence of Mi(a+) may be one in about 430 white people.

No examples were found of blood giving the reaction Mi(a−) Vw+; this phenotype could only have been recognized in the 2,071 London samples which were tested with anti-Vw regardless of whether they were Mi(a+) or Mi(a−).

INHERITANCE

The samples for the genetic investigation came from the families of Mi(a+) people in table 1 and from those found in Buffalo. The great majority of the family samples were collected in Buffalo and in Glasgow; they were sent to London where they were further tested with anti-M, anti-N, anti-S, anti-s and anti-Vw.

The family samples were also tested for the A_1A_2BO, P, Rh, Lutheran, Kell, Lewis and Duffy groups; about half of them were also tested for the Kidd groups.

TABLE 1. RESULTS OF TESTS WITH ANTI-Mi^a AND ANTI-Vw ON RANDOM WHITE PEOPLE

	Mi(a+) Vw+	Mi(a+)Vw−	Mi(a−) Vw+	Mi(a−) Vw−	Total
London	2	1	0	2068	2071
Glasgow	1	5	1767		1773
Total	3	6	3835		3844

As a result one extra-marital child was recognized and discounted. No association of the antigens Mi^a and Vw with any of these groups was expected, nor was it found.

Inheritance of Mi(a+) Vw+

The families in figure 1 all show that the phenotype Mi(a+) Vw+ is inherited as a dominant Mendelian character.

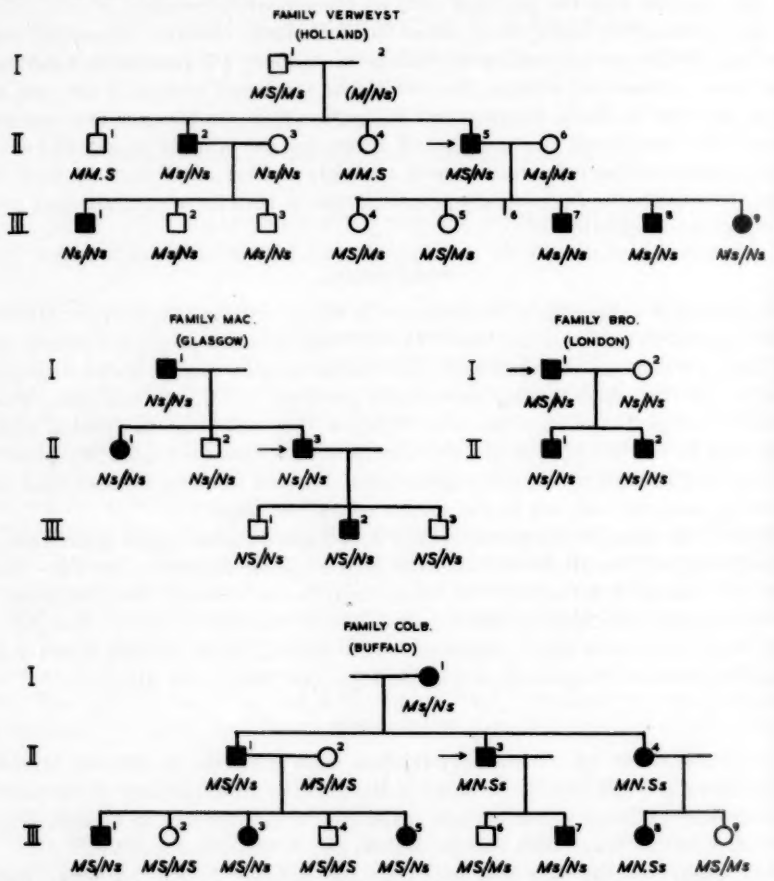

FIG. 1. Families illustrating the inheritance of the phenotype Mi(a+) Vw+. Black = Mi(a+) Vw+: white = Mi(a−) Vw−. Arrow = propositus. In three of the four families (Verweyst, Bro. and Colb.) the gene responsible for the Mi(a+) Vw+ reaction is seen travelling with *Ns*. The family Mac. gives no linkage information.

The groups have been written as genotypes wherever this is disclosed by the serological tests or by the combined evidence of serological tests and the groups of other members of the family. When the groups of missing people have been deduced they are given in brackets. Antisera used: anti-Mi^a, anti-Vw, anti-M, -N, -S, -s. Samples from the original Vw family, Verweyst, were kindly sent by Dr. van Loghem. In this family II-1 and II-4 have not been tested with anti-s and III-9 has not been tested with anti-Mi^a or anti-s.

In family Verweyst, the MNSs groups are such that it can be seen that the gene responsible for the Mi(a+) Vw+ reaction is travelling on an *Ns* chromosome which must have come from the late grandmother, I-2. In generation II, the two Mi(a+) Vw+ children have received their mother's *Ns* while the two Mi(a−) Vw− children have received her *M*; in generation III, all four Mi(a+) Vw+ children have received the grandmaternal *Ns* while all four Mi(a−) Vw− children have received a grandpaternal *Ms* or *MS*. Thus, there are 12 non-cross-overs and no cross-over.

In the family Bro., both Mi(a+) Vw+ children have received their father's *Ns*; so the family provides 2 more non-cross-overs.

In family Colb., the MNSs groups are such that only the offspring of II-1 and II-2 give direct evidence of linkage; their three Mi(a+) Vw+ children have received their father's *Ns* while the two Mi(a−) Vw− have received their father's *MS*. Therefore, this family provides 5 more non-cross-overs and no cross-over. (If we applied the linkage knowledge we could write the genotypes of II-3, II-4 and III-8 as *MS/Ns*.)

Family Mac. gives no information about linkage because I-1 and II-3 are both homozygous *Ns/Ns*. But now that the linkage is established this family shows that once again the gene responsible for the Mi(a+) Vw+ reaction is carried on a *Ns* chromosome. Yet another example is provided by a Mi(a+) Vw+ *Ns/Ns* person in table 1 whose family has not been tested.

The families in figure 1, therefore, establish linkage between the gene responsible for the Mi(a+) Vw+ reaction and the *MNSs* genes. They contain in all 19 non-cross-overs and no cross-over. In five unrelated white people the particular alignment of the new gene with the *MNSs* genes has been made clear, and in each case, the new gene is on an *Ns* chromosome. The probability of this apparent preference for *Ns* being due merely to chance is less than one in a hundred, so there is evidently a marked predilection for partners. This shows that the linkage is not of the traditional kind, with more or less frequent crossing-over resulting in equilibrium, but of the special kind found between the *CDE* genes of the Rh system and between the *MN* and *Ss* genes, in which crossing-over must be a very rare event indeed. We presume that other alignments will be found.

The Mi(a+) Vw+ child III-9 in family Verweyst (figure 1) died at birth. As her cells were sensitized with her mother's anti-Vw, the antigen must be well developed before birth (Hart *et al.*, 1954).

Inheritance of Mi(a+) Vw−

The families in figure 2 show that the phenotype Mi(a+) Vw− is inherited as a dominant Mendelian character.

Four of the families, Hut., Col., Pul. and Erm., prove the existence of linkage between the gene responsible for the Mi(a+) Vw− reaction with the *MNSs* genes.

In family Hut., all the Mi(a+) Vw− people possess the *MS* chromosome of I-2. In this family there are 10 non-cross-overs and no cross-over.

The reconstruction of the groups of I-2, who is dead, may be used as an example of the deductive method that frequently has to be resorted to in translating MNSs phenotypes into genotypes.

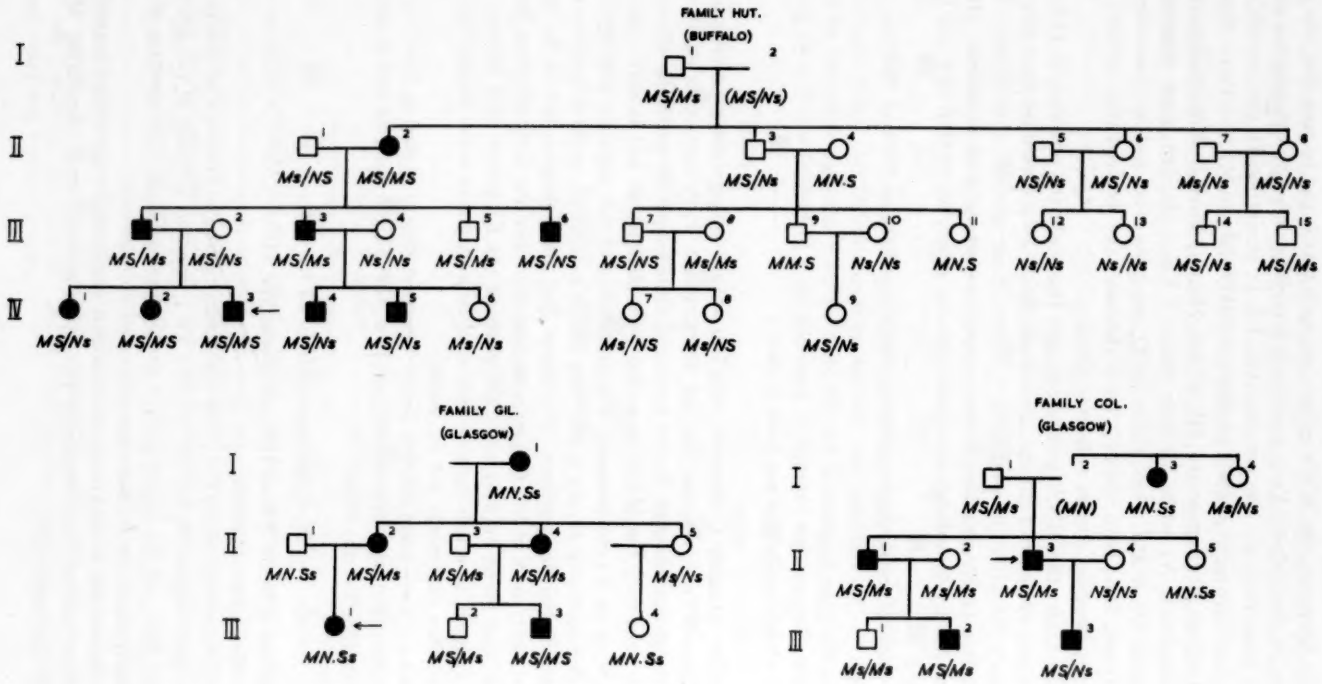
FAMILY HUT.
(BUFFALO)
I
II
III
IV
MS/Ms
(MS/Ns)
Ms/NS
MS/MS
MS/Ns
MN.S
NS/Ns
MS/Ns
Ms/Ns
MS/Ns
MS/Ms
MS/Ns
Ns/Ns
MS/Ms
MS/NS
MS/NS
Ms/Ms
MM.S
Ns/Ns
MN.S
Ns/Ns
Ns/Ns
MS/Ns
MS/Ms
MS/Ns
MS/MS
MS/MS
MS/Ns
MS/Ns
Ms/Ns
Ms/NS
Ms/NS
MS/Ns
FAMILY GIL.
(GLASGOW)
MN.Ss
MN.Ss
MS/Ms
MS/Ms
MS/Ms
Ms/Ns
MN.Ss
MS/Ms
MS/MS
MN.Ss
FAMILY COL.
(GLASGOW)
MS/Ms
(MN)
MN.Ss
Ms/Ns
MS/Ms
Ms/Ms
MS/Ms
Ns/Ns
MN.Ss
Ms/Ms
MS/Ms
MS/Ns

FIG. 2.

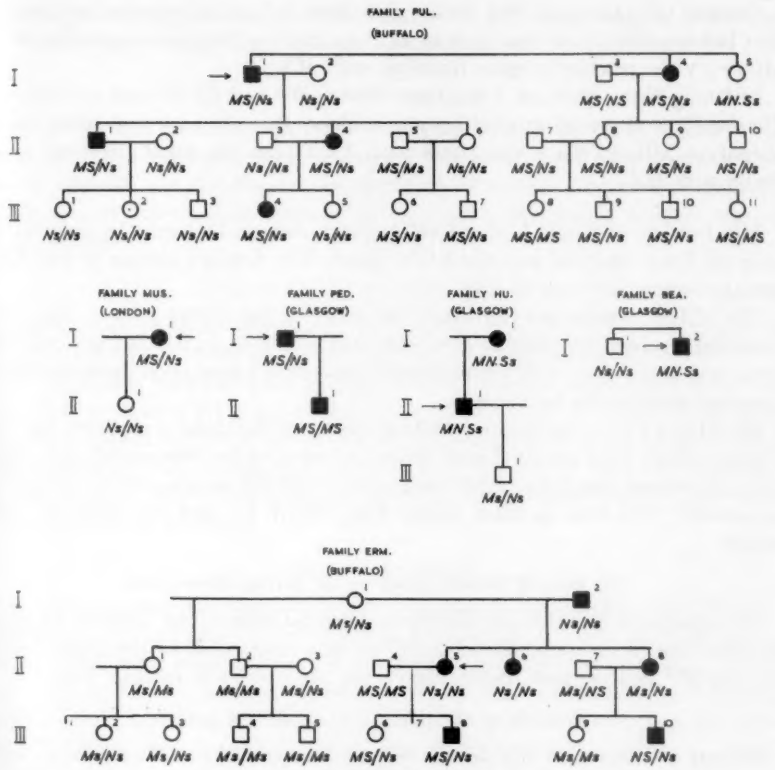

FIG. 2. (*Continued*)

FIG. 2. Families illustrating the inheritance of the phenotype Mi(a+) Vw−. Black = Mi(a+) Vw−: white = Mi(a−) Vw−. Arrow = propositus. In three of the nine families (Hut., Col. and Pul.) the gene for the Mi(a+) Vw− reaction is seen travelling with *MS*. Family Erm., on the other hand, shows the gene travelling with *Ns*. For other notes see legend to Figure 1. In family Hut. II-3, II-4 and their issue were not tested with anti-s.

II-2 is of the genotype *MS/MS*; I-2, therefore, has a chromosome *MS*. III-12 and III-13 have the phenotype Ns; therefore, theis genotypes are *Ns/Ns*; therefore, II-6 whose phenotype is MNSs, must be of the genotype *MS/Ns*; and her *Ns* chromosome must have come from I-2 whose genotype is, therefore, *MS/Ns*. That I-2 has *Ns* may also be deduced if the argument begins with III-15. This illustrates the occasional importance of testing rather unpromising branches of a family which lack the character being studied.

In family Col., again the linkage is with *MS*. We consider that there are 5 non-cross-overs and no cross-over. The argument begins with III-3 but it is rather involved and scarcely worth giving in view of the other overwhelming evidence for linkage.

In family Pul., the linkage again is with *MS* and there are 11 non-cross-overs and no cross-over.

Families Gil., Mus. and Ped. do not give direct linkage information but, knowing that linkage exists, it is clear that in all three families the gene responsible for the Mi(a+) Vw− reaction is again travelling with *MS*.

In family Erm., there are 2 non-cross-overs (III-9 and III-10) and no cross-over. The family is of special interest because it shows that the gene responsible for the phenotype Mi(a+) Vw− can travel with *Ns*, though the usual alignment is evidently with *MS*.

The families of figure 2, therefore, establish linkage between the gene for the Mi(a+) Vw− reaction and the *MNSs* genes. The families contain a total of 28 non-cross-overs and no cross-over.

The *MNSs* chromosome on which the gene for the Mi(a+) Vw− reaction is travelling has been identified in seven unrelated people; in six it is *MS* and in one *Ns*. Since only 25 per cent of all white chromosomes are *MS* here again there is evidently a marked predilection for partners.

The Mi(a+) Vw− reaction is well developed at birth (Mohn *et al.*, 1958). In figure 2, family Hut., IV-3 and IV-5 were tested as cord samples. Presumably the antigen also is developed long before birth because IV-3 suffered from hemolytic disease due to anti-Mi^a. The tests on III-8, family Erm. (figure 2), were also done on a cord sample.

The place of the new genes on the MNSs *chromosome*

This appears to be a difficult problem and it is far from solved. The discussion will be made easier if we are permitted to call the gene responsible for the Mi(a+) Vw− reaction *Mi*^{a} and the gene responsible for the Mi(a+) Vw+ reaction *Vw*.

Relation of Mi^a *and* Vw *to the* MNSs *genes*

At least it seems clear that neither *Mi*^{a} nor *Vw* are alleles or *M* or *N* or of *S* or *s*. Several Mi(a+) Vw− and Mi(a+) Vw+ people have been found to be of the phenotype MNSs and their M, N, S and s antigens were indistinguishable from normal ones, judged by their reactions with the corresponding antisera.

Since *M*^{c} (Dunsford *et al.*, 1953) and *M*^{g} (Allen *et al.*, 1958) are alleles of *M* and *N* they could hardly be specially related to *Mi*^{a} and *Vw*. Furthermore, samples of blood of the phenotype Mi(a+) Vw− and Mi(a+) Vw+ have been tested with anti-M and anti-N sera capable of detecting M^c—with negative results, and samples have been tested with anti-M^g—also with negative results.

Since *S*^{u} is an allele of *S* and *s*, it could hardly be specially related to *Mi*^{a} and *Vw*. This is supported by the fact that two *S*^{u}*S*^{u} people have been tested with anti-Mi^a and three with anti-Vw and found to be negative.

The theoretical possibility that the Mi(a+) Vw− and Mi(a+) Vw+ phenotypes are the result of interaction between the *MNSs* genes appears to be ruled out by the rarity of the phenotypes and by the fact that *Mi*^{a} has been identified both on the chromosome *MS* and *Ns*.

Relation to the Hunter and Henshaw genes

The antigens Mi^a and Vw are not the same as the antigens Hu or He. The blood of several white people Mi(a+) Vw+ and Mi(a+) Vw− has been tested with anti-Hu

and anti-He with negative results. The genes *Mi*^{a} or *Vw* could be alleles of *Hu* or of *He*; the rare families that could give information have yet to be found.

Relation to the gene Vr

Neither Mi^a nor Vw is the same as the antigen Vr (Hart *et al.*, 1958). Mi(a+) Vw+ and Mi(a+) Vw− samples have been tested with anti-Vr and were negative. Conversely, anti-Mi^a and anti-Vw did not react with three Vr+ samples from unrelated people. *Mi*^{a} or *Vw* could be alleles of *Vr* but, again, informative families must be extremely rare.

Relation of Mi^a *and* Vw *to each other*

It seems that we must think of *Mi*^{a} as being related to the *MN* genes in the way that *S* or *s* is related to the *MN* genes and the same may be said of *Vw*.

The serological reactions described below do not help to decide whether *Mi*^{a} and *Vw* are alleles of each other like *C* and *C*^{w} in the Rh system or whether they represent closely linked loci like *C* and *D*. Before this can be decided for certain, it seems that a third antibody is required—either anti-Mi^b or anti-vw and, what is more, a family would be needed of a type of such rarity that it would have to have arisen from experimental matings.

Serological evidence

Obvious questions are whether anti-Mi^a contains two antibodies—anti-Mi^a (in a restricted sense) and anti-Vw, and whether anti-Vw contains only one. Attempts to answer these were made by absorbing anti-Mi^a and anti-Vw sera with Mi(a+) Vw+, Mi(a+) Vw− and, as a control, Mi(a−) Vw− red cells. The results are summarized in table 2. The absorptions were done at 20°C. and so were the subsequent titration tests; the cells for these tests were suspended in saline.

Though there appears to be a good deal of cross-absorption, the evidence strongly suggests that the serum Hut. contains two antibodies, anti-Mi^a (in the restricted sense) and anti-Vw. Comparative tests at different temperatures and tests using

TABLE 2. RESULTS OF ABSORBING TWO EXAMPLES OF ANTI-Mi^a AND ONE EXAMPLE OF ANTI-Vw WITH Mi(a+) Vw+, Mi(a+) Vw−, AND Mi(a−) Vw− RED CELLS

Sera		Absorbed by ½ vol. of Packed Cells	Titration Scores: Mi(a+) Vw+ cells	Mi(a+) Vw− cells	Interpretation
anti-Mi^a (Hut.)	×	Mi(a−) Vw−	60	43	anti-Mi^a + Vw
anti-Mi^a (Hut.)	×	Mi(a+) Vw+	0	15	anti-Mi^a
anti-Mi^a (Hut.)	×	Mi(a+) Vw+ twice	0	11	anti-Mi^a
anti-Mi^a (Hut.)	×	Mi(a+) Vw−	11	0	anti-Vw
anti-Mi^a (Dal.)	×	Mi(a−) Vw−	13	20	anti-Mi^a + Vw
anti-Mi^a (Dal.)	×	Mi(a+) Vw+	0	13	anti-Mi^a
anti-Mi^a (Dal.)	×	Mi(a+) Vw−	0	0	
anti-Vw (Verw.)	×	Mi(a−) Vw−	27	0	anti-Vw
anti-Vw (Verw.)	×	Mi(a+) Vw+	2	0	
anti-Vw (Verw.)	×	Mi(a+) Vw−	27	0	anti-Vw
			Vw	Mi^a	antigens

TABLE 3. THE SOURCES OF CERTAIN ANTI-Mi^a AND ANTI-Vw SERA

Antibody	Donors		Stimulus of Antibody	From
anti-Mi^a	Mrs. Miltenberger	M.S	pregnancy: husband Mi(a+)	Dr. P. Levine
(anti-Mi^a + Vw)	Mrs. Adan.	—	no details	Dr. P. Levine
	Mrs. Hut.	*MS/Ns*	pregnancy: husband Mi(a+) Vw−	Buffalo
	Mrs. Dal.	*Ms/Ns*	no known stimulus	Glasgow
	Mrs. Stev.	*MS/Ms*	no known stimulus	Glasgow
	Mrs. Garl.	*Ms/Ms*	no details	Dr. M. M. Pickles
anti-Vw	Mrs. Verweyst	*Ms/Ms*	pregnancy: husband Mi(a+) Vw+	Dr. J. J. van Loghem
	Mr. Murr.	*MN·Ss*	no known stimulus	Dr. C. Cameron
	Mrs. Bur.	*MN·S*	pregnancy: husband Mi(a+) Vw+	Dr. D. Parkin and Dr. C. Gässer
	1 Donor	*Ms/Ms*	no known stimulus: antibodies found in testing the serum of 703 blood donors	Dr. R. A. Zeitlin
	2 Donors	*MN·Ss*		
	4 Donors	*Ms/Ns*		
	1 Donor	*Ns/Ns*		

different media for the suspension of the red cells (Mohn *et al.*, 1958) give independent support for the presence of two antibodies in serum Hut. That we were not able to achieve an isolation of the anti-Vw in the serum Dal. was due, we suppose, to cross-reaction and to the initial weakness of the antibody.

Anti-Vw, on the other hand, apparently contains but one antibody.

If this interpretation of the antibodies be correct, then only two antigens are needed to fit the pattern of interactions—Vw for blood reacting Mi(a+) Vw+ and Mi^a for blood reacting Mi(a+) Vw−.

Table 3 gives the details, as far as they are known, of the donors of the anti-Mi^a and anti-Vw sera that we have had the opportunity of testing.

If Mi(a+) Vw+ people really have only one antigen, Vw, then we would expect the blood of such people to stimulate anti-Vw free from anti-Mi^a. This is what has happened in families Verweyst and Bur..

If Mi(a+) Vw− people actually possess only one antigen, Mi^a, then we would expect their blood to stimulate anti-Mi^a free from anti-Vw; but, although immunized by a Mi(a+) Vw− fetus, Mrs. Hut. has anti-Mi^a + Vw in her serum (table 2). Indeed, the anti-Vw component in her serum is actually stronger than the anti-Mi^a; but, as the sample was taken in the puerperium, it is possible that the fetus had absorbed enough anti-Mi^a to make the anti-Vw appear the stronger antibody. A sample taken two months later reacted as strongly at 20°C. with Mi(a+) Vw− as with Mi(a+) Vw+ cells suspended in saline.

It is quite possible that the anti-Vw in Mrs. Hut.'s serum was originally present as a "naturally occurring" antibody which probably received some cross-reactive stimulus at the time of her immunization by the antigen Mi^a of her fetus. Anti-Vw is a relatively common antibody; Darnborough (1957) found seven examples in

testing 400 normal sera, and we have confirmed this (see table 3). In our screening of the sera of 703 blood donors, amongst which we found 8 examples of anti-Vw, we disregarded weak reactions and we did the tests at 20°C. More rigorous tests would doubtless have brought to light many more examples of weak anti-Vw.

It is perhaps worth mentioning that in the screening tests the red cells used by Darnborough and by us were of the type Mi(a+) Vw+ which would not be capable of disclosing examples of anti-Mi^a in the restricted sense of the last column of table 2. Such sera would agglutinate Mi(a+) Vw− red cells but not Mi(a+) Vw+ red cells.

Table 3 also shows the MNSs groups, as far as they are known, of the donors of the antisera; they are not in any way remarkable. Darnborough (1957) found that all of the nine donors of anti-Vw were group O. Of the eleven donors of anti-Vw mentioned in table 3, six were A_1, one was A_2, one AB and three were O.

During the course of the work the following "private" antibodies were excluded from being anti-Mi^a or anti-Vw: anti-Di^a, -By, -Wr^a, -Rm and anti-Be^a.

The glimpse they afford of the elaborate structure of the *MNSs* chromosome gives the antigens Mi^a and Vw an interest out of all proportion to their low frequency in the populations so far studied.

SUMMARY

The red cell phenotypes Mi(a+) Vw+ and Mi(a+) Vw− are dominant Mendelian characters. Evidence is produced that each phenotype depends on the presence of a single antigen, Mi(a+) Vw+ reflecting the presence of the antigen Vw, and Mi(a+) Vw− the presence of the antigen Mi^a.

The genes *Vw* and *Mi^a* are part of the *MNSs* complex of genes. In whites *Vw* shows a preference for travelling on an *Ns* chromosome while *Mi^a* shows a preference for travelling on an *MS* chromosome.

The genes *Vw* and *Mi^a* are not alleles of *M* or *N* or of *S* or *s*, whether they are alleles of each other, or of *Hu*, *He* or *Vr* is left in doubt and may remain a problem for a long time.

ACKNOWLEDGMENTS

We are deeply grateful to the following for gifts of antisera used in the investigation —Dr. F. H. Allen, of Boston, Dr. C. Cameron, of Dundee, Dr. Eloise Giblett, of Seattle, Miss van der Hart and Dr. J. J. van Loghem, of Amsterdam, Dr. Philip Levine, of Raritan, Dr. A. E. Mourant, and Dr. Dorothy Parkin, of London, Dr. M. M. Pickles, of Oxford, and Dr. R. A. Zeitlin, of London. Dr. Zeitlin also supplied 2000 of the London blood samples.

We would like to thank the donors and their families for their very kind co-operation. We are much indebted to the following physicians who assisted in obtaining samples of blood from members of the families: Dr. J. B. Atkinson, of Philadelphia, Dr. H. S. Bowman, of Harrisburg, Dr. N. Cote, Dr. J. W. Hurley, Dr. D. L. King, Dr. J. K. Link, Dr. J. M. Steinhart, Dr. Gertrude S. Swarthout, all of Buffalo, and Dr. D. G. Veber, of East Cleveland.

We gratefully acknowledge much technical assistance unstintingly given by Miss Barbara L. Steele of Buffalo and Miss Stella Devine of Glasgow.

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Leukemia and ABO Blood Group[1]

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INTRODUCTION

RECENT INTEREST AND PROGRESS in the investigation of associations between disease incidence and ABO blood group have been summarised by Roberts (1957). The interpretation of such associations, when found, is difficult, but sufficient associations have been demonstrated by statistically sound methods that continued examination of these relationships seems indicated. In the present report, the results of examination of a series of 1387 patients with leukemia are recorded. Buckwalter and others (1956) and Steinberg (1957) have previously reported no evidence of association of leukemia with ABO blood group in studies of 456 patients with leukemia (all forms) and 459 patients with acute leukemia, respectively. The method of selection of one of the comparison samples in the present study may have relevance to studies of ABO groups in other diseases.

MATERIAL

The leukemia series which is the basis of the present study derives from two sources:

(1) An investigation, reported previously (MacMahon and Clark, 1956) of all Brooklyn residents diagnosed as leukemic in the years 1943–52. Blood group was recorded for 66 per cent (1127) of the 1709 total patients. The determination and recording of the blood group in most cases was prompted solely by the patient's need of transfusion, and consequently varied with the clinical course and type of leukemia. The 1127 patients are therefore not representative of the total 1709. For example, blood group was recorded for 69 per cent (529) of the 763 patients with acute leukemia, compared with 56 per cent (229) of the 411 patients with chronic lymphatic leukemia.

(2) All patients with leukemia attending five of the largest Brooklyn hospitals during the years 1953–56. Patients already known through inclusion in the 1943–52 series were excluded. Blood group was known for 76 per cent (260) of the 341 patients from this source.

Comparison samples were drawn from the alphabetical card files of the New York Regional Blood Program of the American Red Cross. These files at the time of sampling included a card for all donors from the New York area who had donated blood through the Red Cross since 1949. Two samples were drawn:

(1) Sample A. A systematic sample assembled by selecting cards at measured in-

Received February 8, 1958.

[1] This study was aided by a field investigation grant (CS9435) from the National Cancer Institute, National Institutes of Health, Public Health Service. One of the authors (John C. Folusiak) was a Medical Student Fellow of the National Foundation for Infantile Paralysis.

tervals throughout the alphabetical files. Only cards referring to residents of Brooklyn and to persons donating blood to this service for the first time were included. The sampling fraction was approximately 1 in 50.

(2) Sample B. A name-matched sample, assembled by selecting for each leukemia patient a donor of the same name. The variables matched were, in order, surname (1232 cases), sex (1121 cases), and first name (308 cases). Choice between several individuals of identical first and last name, where necessary, was on the basis of age matching. First donors were selected in preference to repeat donors, provided a matching surname was obtained. Of the 1232 cases in which the surname could be matched, 1168 were matched by first donors and 64 repeat donors. The donor files contained no donors with surnames to match eleven per cent (155) of the 1387 leukemia patients.

COMPARISON WITH SAMPLE A

The distributions by blood group of the two leukemia series and of the systematic comparison sample are shown in table 1. Since there is no significant difference between the distributions of the two leukemia series, they are combined in subsequent examinations.

The combined leukemia series shows, relative to the comparison sample, a deficiency of group O patients and an excess of groups B and AB. The difference between the two distributions is statistically highly significant. The difference could be accounted for by:

(1) A tendency for leukemia to occur less frequently in persons of group O than in persons of groups B and AB.

(2) A difference between the ethnic compositions of the two series. Such a difference might arise either through ethnic variation in leukemia incidence or because the leukemia series and the blood donor sample were not drawn from the same parent population, i.e. were not representative of the Brooklyn population.

Two ethnic associations of leukemia incidence in the area of the present study have been recognized (MacMahon and Koller, 1957). These are, a low incidence in the

TABLE 1. DISTRIBUTION BY ABO BLOOD GROUP OF 1387 PATIENTS WITH LEUKEMIA, AND A SYSTEMATIC SAMPLE OF BLOOD DONORS (SAMPLE A), BROOKLYN, 1943–56

Blood group	Leukemia Series						Blood donor sample A	
	1943–52		1953–56		Total			
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
O	458	40.6	103	39.6	561	40.4	900	45.8
A	417	37.0	102	39.2	519	37.4	728	37.0
B	179	15.9	44	16.9	223	16.1	261	13.3
AB	73	6.5	11	4.2	84	6.1	78	4.0
Total	1127	100.0	260	99.9	1387	100.0	1967	100.1

Comparison of the two leukemia series:

$$\chi^2 = 1.2,\ n = 3,\ 0.7 < p < 0.8$$

Comparison of the total leukemia series and the blood donor sample:

$$\chi^2 = 16.9,\ n = 3,\ p < 0.001$$

Negro compared to the white population, and a higher rate in the Jewish white population than in non-Jewish whites. The first association is not likely to affect the blood group comparison, since the Negro population of Brooklyn is low (about 7 per cent) and the difference between Negroes and whites in leukemia rates is relatively small (1 to 1.3). However, the second ethnic association of leukemia incidence could well account for differences in ABO distributions. The leukemia rate in the Jewish population is perhaps twice that in the non-Jewish groups, and approximately 35 per cent of the population of the Borough is of Jewish ancestral background. Furthermore, there is, as shown in Table 2, a difference in blood group distribution between the Jewish and non-Jewish leukemia patients. This difference is in the direction necessary to explain the difference between the leukemia series and the comparison sample on the basis of a higher representation of Jews in the leukemia series—that is, compared to the non-Jewish patients, the series of Jewish patients is relatively deficient in persons of group O.

In table 2, the religious affiliation is as recorded by the patient on admission to hospital. Ethnic associations cannot be examined directly in the sample of blood donors, since Red Cross policy precludes the recording of color, religion or other indicators of ancestral background. However, in this area, an idea of ancestral background is frequently suggested by the surname. For 923 of the 1967 donors in Sample A it was considered that the surname was either definitely Jewish or definitely not Jewish (mostly Italian and Irish); 1044 could not be definitely classified. Blood

TABLE 2. DISTRIBUTION OF WHITE PATIENTS WITH LEUKEMIA ACCORDING TO RELIGION AND ABO BLOOD GROUP

Blood group	Jewish		Catholic and Protestant	
	Number	Per cent	Number	Per cent
O	226	34.0	291	45.5
A	261	39.2	235	36.8
B	120	18.0	90	14.1
AB	58	8.7	23	3.6
Total	665	99.9	639	100.0

Religion was unknown for 13 patients.
$\chi^2 = 28.4$, $n = 3$, $p < 0.001$.

TABLE 3. PERCENTAGE DISTRIBUTION OF BLOOD DONOR SAMPLE A ACCORDING TO ABO BLOOD GROUP AND PRESUMED ANCESTRAL BACKGROUND AS JUDGED FROM LAST NAME

Blood group	Names classified as				Total classified		Names not classified	
	Jewish		Non-Jewish					
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
O	142	37.9	281	51.3	423	45.8	477	45.7
A	165	44.0	184	33.6	349	37.8	379	36.3
B	46	12.3	62	11.3	108	11.7	153	14.7
AB	22	5.9	21	3.8	43	4.7	35	3.4
Total	375	100.1	548	100.0	923	100.0	1044	100.1

$\chi^2 = 17.3$, $n = 3$, $p < 0.01$.

group was not known by the person classifying the names. The distributions are shown in Table 3. Once again the marked deficiency of group O in the Jewish group is evident. A considerable relative excess of group A is also seen in the group presumed Jewish.

COMPARISON WITH SAMPLE B

Comparison of the distribution of the Jewish leukemia patients (table 2) with that of the blood donors with Jewish names (table 3), or of the non-Jewish leukemia patients with the blood donors with non-Jewish names would be unsatisfactory since the criteria of ethnic background are different in the samples being compared. A second sample (B) was therefore selected from the blood donor files. Since it was not possible to match this sample with any more reliable index of ethnic background, an attempt was made to match it with the surnames of the leukemia series, as described above. From over 600,000 cards in the blood donor files, it was possible to find a surname match for 88 per cent (1232) of the 1387 leukemia patients. This type of matching, insofar as it is a satisfactory index of ethnic background, will reduce differences between the leukemia and blood donor samples which may result from differences between ethnic groups in frequency of blood donation, as well as those due to ethnic differences in leukemia incidence.

The distributions of the 1232 leukemia patients and their name-matched blood donors are shown in table 4. There is no significant difference between the two distributions. It is concluded that the differences between the leukemia series and the systematic sample of blood donors results from differences between the two series in ethnic representation—probably in relative representation of patients of Jewish ancestral background. This difference probably results from the high incidence of leukemia in the Jewish population of Brooklyn.

TYPE OF LEUKEMIA, AND RH STATUS

The distribution of leukemia patients according to ABO blood group in diagnostic categories is shown in table 5. There is no evidence of statistically significant heterogeneity. The pattern of blood group distribution is more unusual for the 295 patients with chronic granulocytic leukemia than for any of the other major diagnostic categories. However, the distribution of the chronic granulocytic cases does not differ significantly from the distribution of patients with all other diagnoses ($\chi^2 = 5.4$,

TABLE 4. DISTRIBUTION OF 1232 LEUKEMIA PATIENTS AND A NAME-MATCHED SAMPLE OF BLOOD DONORS (SAMPLE B), ACCORDING TO ABO BLOOD GROUP

Blood group	Leukemia patients		Name matched blood donors	
	Number	Per cent	Number	Per cent
O	507	41.2	507	41.2
A	455	36.9	493	40.0
B	193	15.7	166	13.5
AB	77	6.3	66	5.4
Total	1232	100.1	1232	100.1

$\chi^2 = 4.4$, $n = 3$, $0.2 < p < 0.3$.

TABLE 5. DISTRIBUTION ACCORDING TO TYPE OF LEUKEMIA AND ABO BLOOD GROUP

Blood group	Acute		Chronic		Subacute and other	Total
	Granulocytic	Other	Granulocytic	Lymphocytic		
O	159	121	102	108	71	561
A	144	102	120	106	47	519
B	66	35	53	48	21	223
AB	15	13	20	23	13	84
Total	384	271	295	285	152	1387

$\chi^2 = 18.6$, $n = 12$, $p \simeq 0.1$.

TABLE 6. DISTRIBUTION OF LEUKEMIA SERIES AND COMPARISON SAMPLES ACCORDING TO Rh STATUS

Type of leukemia	Number		Total	Per cent Rh negative
	Rh neg.	Rh pos.		
Acute granulocytic	280	25	305	8.2
Other acute forms	188	21	209	10.0
Chronic granulocytic	210	23	233	9.9
Chronic lymphocytic	202	25	227	11.0
Other	101	15	116	12.9
Total	981	109	1090	10.0
Comparison sample A	1747	220	1967	11.2
Comparison sample B	1083	149	1232	12.1

$n = 3$, $0.1 < p < 0.2$). It would nevertheless seem desirable to record further data, when available, on the comparison of the ABO distributions of series of leukemia patients according to specific type of leukemia.

Distributions according to Rh status are recorded in table 6. There are no significant differences between the percentages of Rh negative patients in any of the groups examined.

DISCUSSION

The most obvious deficiency of the present study is the possibility of bias arising from the fact that data on blood group were obtained for only 68 per cent of the total series of leukemia patients. However, to affect the results of the examination it would be necessary for the probability of transfusion (and hence of recording of blood type) to be related to ABO group. The material has been examined for evidence of variation between patients of different blood groups in the duration of symptoms prior to diagnosis and in the clinical nature of the presenting symptoms. No such variation was evident. No relationship was found between ABO blood group and the length of survival of patients with the acute leukemias (MacMahon and Forman, 1957). For the chronic leukemias it was noted that duration is significantly longer for patients of group B than for patients of other groups (Feinleib and MacMahon, 1958). However, it is difficult to see how this latter finding could affect the specific results noted in the present study.

Of incidental interest to the negative findings in the leukemia data, are the differences in blood group distribution noted between the Jewish and non-Jewish populations of Brooklyn, and the fact that these differences are readily detectable when surname is used as an index of ethnic background. Roberts (1942) noted differences in blood group distribution on the basis of surname in Wales. The possibility exists of using surname matching, as here described, to differentiate blood group associations of disease occurring secondary to ethnic associations from those more directly related to blood group. This method, if practicable, would be less time consuming than the sibship studies as used by Clarke et al. (1956). However, the applications of surname matching are obviously limited to the examination of ethnic associations which are clearly indicated by surname, and to geographic areas and time periods in which such surname-identification persists. It should be noted in addition that sibship studies also provide a mechanism of elimination of maternal effects and non-racial stratification not provided by surname matching.

SUMMARY

Data are recorded on the ABO blood group of 1387 patients with leukemia diagnosed in Brooklyn between 1943 and 1956. By comparison with a systematic sample of Brooklyn blood donors, the leukemia series was deficient in persons of group O. It was noted, however, that both in the leukemia series and in the blood donor sample there was a lower percentage of patients of group O among Jewish than among non-Jewish groups. Since leukemia is twice as frequent in the Jewish as in the non-Jewish population of Brooklyn, this is a ready explanation of the relative deficiency of persons of group O in the leukemia series. This explanation is supported by the observation that the distribution of the leukemia series by ABO blood group did not differ significantly from that of a sample of blood donors matched to the surnames of the leukemia patients.

ACKNOWLEDGEMENTS

For access to case records the authors are indebted to the administrative, medical, and record staffs of many New York City hospitals, a list of which has been published previously (MacMahon and Clark, 1956). Hospitals providing additional data (1953–56) were Coney Island Hospital, Jewish Hospital of Brooklyn, Kings County Hospital, Long Island College Hospital and Maimonides Hospital of Brooklyn. We are indebted to Dr. Victor Ginsberg, the Director, for access to the extensive records of the Kings County Hospital Blood Bank.

The New York Regional Blood Program of the American Red Cross gave ready access to records and we are indebted to Dr. W. Markal and Dr. Mary Boynton for facilitating that portion of the study.

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Empirical Risks in Consanguineous Marriages: Sex Ratio, Malformation, and Viability[1]

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WITHIN THE LAST DECADE, it has become increasingly apparent that the population genetics of man could and perforce must be explored. The need for information regarding selection, spontaneous mutation rates, etc. in human populations has been most forcefully demonstrated, perhaps, by recent attempts to evaluate the threat to mankind posed by the advent of nuclear energy as a source of power both in peace and in war. While data of a sort exist on the dynamics of human populations, much of the information available is, for one reason or another, unsuited to the needs of the population geneticist. Of late, exploration of certain aspects of human population genetics, notably the consequences of inbreeding, has attracted increasing attention.

The purposes of the present paper are to describe the effects of inbreeding on the sex ratio, the frequency of major congenital malformations, stillbirths, neonatal deaths, and infantile deaths in Japan. The study to be reported is perhaps unique in a number of respects, namely, (1) the prospective orientation of the study, (2) the size of the sample, and (3) the fact that critical observations were, in the main, made by trained observers, usually physicians, and are not dependent upon recall.

MARRIAGE PRACTICES IN JAPAN

Traditionally, the ideal ages at marriage in Japan are 24 (for boys) and 23 (for girls), and in point of fact, most individuals are either married or negotiating a marriage by 25[2]. There are, of course, a number of considerations, the most important being economic, affecting age at marriage. To some of these considerations we shall return in a moment. But first, we shall address ourselves briefly to three practices common in Japan, namely, (1) the "adoptive son marriage", (2) the affinous marriage, and (3) the consanguineous marriage. The first two of these have an immediate bearing on the frequency of marriages between related persons, and the types of errors which may arise in recording consanguinity in Japan.

Received December 5, 1957.

[1] This work was sponsored by the Atomic Bomb Casualty Commission, Field Agency of the National Academy of Sciences-National Research Council of the United States and the National Institute of Health of Japan. Analysis of these data was sponsored by the Atomic Energy Commission under a grant to the University of Michigan (Contract AT (11-1)-405).

[2] Under the old Civil Code of Japan (effective to 1947), parental consent was required for a son to marry before the age of 30, or a daughter before the age of 25 (Article 772, 1). If marriage occurred without consent, the head of the family could legally expel from the family the offending person or persons (Article 750). At present, parental consent is required only for marriages involving minors (under the age of 21). For details of these provisions of the Civil Codes see Steiner, 1950.

"*Adoptive son marriage*":—Pride in family name is not a characteristic limited to the Japanese, but attempts to ensure the perpetuation of the family name have led to marriage customs in Japan which are uncommon in the United States and Western Europe. In most countries, attempts to perpetuate the family name by means other than through the normal pattern of biologic descent involve the adoption, at a tender age, of a male heir. This practice is, of course, to be found in Japan (the adoptive son is termed a *yōshi*), but an oft-employed alternate is the so-called "adoptive son marriage." Two legal types of such marriage were recognized under the old Civil Code (effective to 1947). These were the ***nyūfu*** (entering husband) marriage, and the ***muko-yōshi*** (bridegroom-adoptive son) marriage. The distinction between these types has been clearly drawn by Hozumi (1933). Briefly, it is as follows: In Japan, the headship of a kindred normally passes from eldest son to eldest son. Occasionally the eldest son may be without issue in which case the headship, upon the death of the eldest son, passes through the next oldest son. If the eldest son has only daughters, the eldest daughter is, at least nominally, the head of the kindred. The latter occurrence, however, poses a problem at the time of marriage since normally a wife is enrolled in the ***koseki*** (household record) of her husband. That is to say, she takes the family name of her husband. In the event that the prospective wife was a household head, the normal convention would create many difficulties. To circumvent these difficulties, two alternatives are available to the female household head. She may select her spouse from among her male relatives having the same family name, in which case the headship does not leave the family. Or, if she selects her spouse from outside her kindred, he may be enrolled in the kindred of his wife. The term ***nyūfu*** marriage is applied to either of these alternatives, and in neither case does the female relinquish the headship of the kindred. This procedure need not be restricted to female household heads; however, consanguineous marriages are proportionally more frequent among heads of families. Thus, in a small section, Aza Takenoedao, of Shībamura, Yoshida and Yanase (1951) found that among 32 marriages involving heads of families 56.5 per cent were consanguineous, whereas, among 50 marriages of adult males and 64 marriages of adult females selected without reference to whether the individual was or was not a head of family, 44.0 and 31.3 per cent, respectively, were consanguineous.

In the ***muko-yōshi*** marriage, the adopted son is married to a daughter, generally the eldest, of the adoptive parent at the time of adoption. This is a legal act which combines marriage and adoption. The headship of the family is then vested in the adopted bridegroom-son.

Neither the ***nyūfu*** nor the ***muko-yōshi*** marriage is uncommon as can be seen from Table 1 where the frequencies of these marriages are given for all of Japan as well as selected areas. These types of marriages appear to be on the decline; for example, in 1916, 62.1 in every thousand marriages were a ***muko-yōshi*** whereas by 1934 this requency had dropped to 51.8.

Our interest in these marriages stems from the fact that the husband is frequently drawn from collateral branches of the family, and consequently the practice of the "adoptive son marriage" tends to enhance the frequency of consanguineous marriages.

TABLE 1. THE FREQUENCY OF "ADOPTIVE SON MARRIAGES" IN JAPAN (DATA DRAWN FROM NIHON TEIKOKU TOKEI NENKAN, 1931; NIHON TEIKOKU JINKO DOTAI TOKEI, 1931, 1934; AND NIHON TEIKOKU JINKO DOTAI TOKEI KIJUTSU-HEN, 1936). SEE TEXT FOR FURTHER EXPLANATION.

Year	Region	Nyūfu marriage		Muko-yōshi marriage		Other marriages	Total marriages
1931	Nagasaki Prefecture	191	2.1	321	3.5	8,534	9,046
	Nagasaki City	26	2.0	51	3.9	1,233	1,310
	Hiroshima Prefecture	362	2.5	610	4.2	13,594	14,566
	Hiroshima City	31	1.6	48	2.5	1,846	1,925
	All Japan	12,687	2.6	26,539	5.3	457,348	496,574
1936	Nagasaki Prefecture	201	2.1	321	3.4	8,899	9,421
	Nagasaki City	26	1.8	59	4.1	1,343	1,428
	Hiroshima Prefecture	297	2.0	630	4.3	13,617	14,544
	Hiroshima City	49	2.6	48	2.5	1,809	1,906
	All Japan	12,560	2.4	26,562	5.2	473,532	512,654

It would, however, be misleading to leave the impression that all, or even a substantial part of, adoptive son marriages are to ensure perpetuation of the family name. While this is undoubtedly an important factor in the middle and upper economic levels, among members of the lower economic strata, the bulk of whom have had family names only since about 1875, perpetuation of family name is far less important than economic security in motivating adoptive son marriages. In Japan, one's children, and particularly the males, are one's security in old age. Accordingly, parents with only daughters will frequently adopt a son, in one of the manners described, as a buttress against the day when they, the parents, are no longer capable of supporting themselves. While the frequency of this latter event is not known, the consensus of opinion among Japanese interested in marital practices is that it is high.

Affinous marriages:—Individuals related by ties of marriage and not blood or descent are said to be affinal relatives, and marriage between two such persons is termed an affinous marriage. Affinous marriages can be of two distinct types based upon whether or not a concomitant of affinity is remarriage. Type A affinous marriages, where remarriage is not a concomitant, would include marriages such as brothers- with sisters-in-law. The genetic extreme of this type of union would be the marriage of identical twins with identical twins. Type B affinous marriages comprise unions of in-law relatives, and involve remarriage of at least one of the partners; these marriages have been classified as first degree when the second marriage involved a brother- or sister-in-law, or second degree, when the second union involved a niece- or nephew-in-law. The levirate marriage, the marriage of a widow to the brother of her deceased spouse, or the sororate marriage, the marriage of a widower to the sister of his deceased spouse, are generally instances of Type B, first degree, affinous marriage; it is not mandatory, however, in the levirate or sororate marriage that wife and husband be unrelated.

The two types of affinous marriages have met with different social barriers in different societies. Neither in Japan nor in Judaeo-Christian societies does there appear to have been an explicit prohibition of the Type A affinous marriage. The situation is somewhat different with respect to the Type B marriage. In Judaeo-Christian

societies, these marriages have been banned since the Old Testament wherein there is a specific admonition "Thou shalt not covet thy brother's wife" (Leviticus 18:6–30). No such prohibition or admonition exists for the Japanese.

In-law or affinous marriages are rather frequent occurrences in Japan. Kida et al. (1949), in a survey of marriage practices in Kyushu, report that in-law marriages represent 2.8 per cent of all marriages encountered in their survey. Their data are reproduced in Table 2. Roman Catholic church records in Nagasaki reveal a similar frequency, 2.5 per cent, for the years 1945–1949 (Schull, unpublished data).

Aoyama (1948), in a post war study of remarriage among war widows, has called attention to the frequency of levirate marriages in Japan. Among 92 remarried widows, in 55 cases the second husband was a brother of the deceased spouse; in the remaining 37 cases the second spouse was either unrelated to the first (33 cases) or was a relative other than a sibling (4 cases). Of the 55 marriages involving a brother of the deceased husband, in 52 instances the brother was younger than the deceased husband. The frequency of this event reflects the Japanese view of family responsibilities. Upon the death of an elder, married brother, the burden of support of the widow frequently falls upon one of her unmarried brothers-in-law. The latter individual then faces a dilemma—on the one hand, he must support his brother's wife, and, on the other hand, he desires a wife but generally cannot support two women. A satisfactory solution to this dilemma is obtained if he marries his brother's widow. This convention would tend to maintain a consanguineous union if the deceased brother had selected a relative as a wife, or conversely, to discourage a consanguineous marriage if the deceased brother had selected an unrelated individual as his spouse.

Consanguineous marriages:—Though the high frequency of consanguineous marriages in Japan is now a matter of common knowledge, a few words regarding the

TABLE 2. THE FREQUENCY OF AFFINOUS MARRIAGES IN KUMAMOTO PREFECTURE (AFTER KIDA ET AL., 1949)

Region	Number of couples investigated	Type A affinous marriage	Type B affinous marriage*	Other in-law marriage	Possible in-law marriage**	Total affinous marriages	
						#	%
Kumamoto City	1,830	11	3	31	6	45	2.5
Yamaga	2,902	22	7	71	3	100	3.4
Kumafu	2,908	19	6	54	5	79	2.7
Udo	1,092	4	3	27	2	34	3.1
Toride	459	2	2	15	0	19	4.1
Hanabusa	390	5	5	5	0	15	3.8
Kikuchi	888	9	2	13	1	24	2.7
Asahino	416	4	3	8	3	15	3.6
Mizuminato	776	7	3	9	1	19	2.4
Nagashima (Higashi)	1,788	7	0	28	6	35	2.0
Nagashima (Nishi)	1,433	5	5	15	14	25	1.7
Total	14,882	95	39	276	41	410	2.8

* Presumably these figures include only the first two degrees of Type B affinous marriages.
** These uncertain relationships are not included in the totals.

frequency of consanguineous marriages and the attitudes toward these marriages seem essential to an understanding of the data to be presented subsequently.

There is known to the author no nation-wide survey of the proportion of all marriages which are consanguineous in Japan; however, Japanese sociologists and demographers generally assert that some 4–5 per cent of marriages in Japan are between first cousins (see Okazaki, 1941). A brief, and by no means exhaustive, summary of the frequencies of consanguinity thus far reported in 11 of the 46 prefectures of Japan is given in Table 3.

Perhaps the most striking feature of these data is the persistence of high rates of inbreeding in urban centers such as Kumamoto or Tokyo. On the face of the evidence, it would not appear that the association of frequency of consanguineous marriages with size of municipality holds over the range of municipality sizes. For example, the frequencies of first-cousin marriages in Kure (pop. 187,775), Hiroshima (285,712), Nagasaki (241,638), Kumamoto (267,506), and Tokyo (5,385,071) differ only by a factor of two despite the fact that population size, in 1950, varies by as much as thirty-fold. There is much cultural evidence to suggest, however, that the larger cities are merely aggregations of villages. The rates of consanguinity in urban centers would support this general notion since the frequency of consanguineous marriages seems to plateau once a certain city size is attained. One cannot approach this argument with much rigor, however, since many of the marriages encountered in urban areas will have been contracted before migration to the city, or arranged after migration with someone from the village of origin. The "true" incidence of consanguineous marriage within urban "isolates" in Japan is unknown.

Considerable effort on the part of Japanese investigators has been expended on the studies of the so-called "consanguinity villages" to be found scattered throughout Japan. Among such villages which have been studied are Narata (Nishiyama-mura, Yamanashi Prefecture; Shinozaki, 1955), Gokanosho (Kumamoto Prefecture; Kida et al., 1949; Kanokogi, 1952; Kanokogi and Kaku, 1952), Shība (Miyazaki Prefecture; Yanase, 1949, 1951), Ōaza Tsuru (Umibe-mura, Oita Prefecture; Ikemi, 1936), and Aza Maruyama (Shinmaru-mura, Ishikawa Prefecture; Maruyama et al., 1935). The origins of these mountain villages, insofar as they are known, read like footnotes to Japanese history. Narata, for example, is said to have been founded in the Nara Era during the reign of the Empress Koken (about 1200 years ago). Legend has it that the Empress had fallen ill, and, in a fever-racked dream, saw a hot spring with curative powers located in the northern part of the country. Immediately she dispatched some of her retainers to search for this miraculous spring. The spring, which these men found and were charged to guard in perpetuity, as it were, is now called Nishiyama onsen. The present villagers are alleged to be the descendants of the guardsmen and their families who because of their isolation intermarried generation after generation. Needless to say, it has not been possible to authenticate this charming legend although a fairly reliable village history extending back some 400 years does exist. That the legend may not be entirely the figment of some vivid imagination is suggested by the language of the villagers, ***narata kotoba***, which differs substantially from the language spoken in adjacent areas, the earthenware produced in the village, which is like that produced in the Nara Era, and the structure of the

TABLE 3. THE FREQUENCY OF CONSANGUINEOUS MARRIAGES IN VARIOUS PARTS OF JAPAN

Prefecture	Village or Town	Number of couples Investigated	Consanguineous marriages		First cousin marriages		1½ Cousin		Second Cousin		Investigator
			#	%	#	%	#	%	#	%	
Fukushima	Okisawa	483	59	12.2	38	7.9	9	1.9	12	2.5	Ichiba, 1953
	Koizumi	173	18	10.4	15	8.7	1	0.6	2	1.2	" "
Nagano	Ono	624	131	21.0	81	13.0	16	2.6	34	5.5	Kubota et al.,
	Kawajima	414	117	28.3	68	16.4	15	3.6	34	8.2	1950
	Tatsuno	2,195	279	12.7	172	7.8	24	1.1	83	3.8	" "
	Asahi	1,148	160	13.9	99	8.6	19	1.7	42	3.7	" "
	Nakaminowa	2,551	380	14.9	235	9.2	33	1.3	112	4.4	" "
	Higashi Minowa	625	110	17.6	61	9.8	17	2.7	32	5.1	" "
	Minowa	506	66	13.0	47	9.3	4	0.8	15	3.0	" "
	Fujisawa	663	159	24.0	95	14.3	14	2.1	50	7.5	" "
	Nishi Minowa	1,069	208	19.5	134	12.5	28	2.6	46	4.3	" "
	Minami Minowa	891	127	14.3	83	9.3	13	1.5	31	3.5	" "
	Tera	726	123	16.9	83	11.4	13	1.8	27	3.7	" "
	Nagafuji	420	75	17.9	47	11.2	9	2.1	19	4.5	" "
	Miyoshi	400	107	26.8	56	14.0	10	2.5	41	10.3	" "
	Miwa	727	147	20.2	68	9.4	10	1.4	69	9.5	" "
	Nagato	662	63	9.5	44	6.6	8	1.2	11	1.7	" "
	Inacho	3,353	381	11.4	238	7.1	45	1.3	98	2.9	" "
	Nishi Haruchika	1,029	159	15.5	97	9.4	26	2.5	36	3.5	" "
	Midori	734	143	19.5	86	11.7	15	2.0	42	5.7	" "
	Tomigata	990	169	17.1	100	10.1	20	2.0	49	4.9	" "
	Kanname	476	80	16.8	57	12.0	5	1.1	18	3.8	" "
	Miyata	760	129	17.0	81	10.7	15	2.0	33	4.3	" "
	Higashi Haruchika	732	154	21.0	94	12.8	15	2.1	45	6.1	" "
	Ina Mura	372	80	21.5	55	14.8	10	2.7	15	4.0	" "
	Inasato	417	89	21.3	54	12.9	10	2.4	25	6.0	" "
	Nakazawa	1,312	216	16.5	146	11.1	24	1.8	46	3.5	" "
	Nomukai	797	135	16.9	89	11.2	17	2.1	29	3.6	" "
	Akaho	3,195	424	13.3	283	8.9	44	1.4	97	3.0	" "
	Kamikatagiri	624	74	11.9	45	7.2	9	1.4	20	3.2	" "
	Iijimi	1,327	178	13.4	118	8.9	16	1.2	44	3.3	" "
	Nanakubo	601	105	17.5	63	10.5	11	1.8	31	5.2	" "
	Katagiri	644	123	19.1	83	12.9	16	2.5	24	3.7	" "
	Nakata machi	805	57	7.1	48	6.0	2	0.2	7	0.9	Kishimoto, 1954
Aomori	Narusawa	335	9	2.7	8	2.4	1	0.3	0	0	Ichiba, 1953
Chiba	Tsuchi	1,314	17	1.3	10	0.8	1	0.1	6	0.5	" "
Fukuoka	Shigazima-mura	349	59	16.9	33	9.5	5	1.4	15	4.3	Yanase, 1951
Gifu	Tokuyama-mura	49	15	30.6	13	26.5	0	0	2	4.1	Kishimoto, 1954
	Takane-mura	101	5	5.0	5	5.0	0	0	0	0	" "
	Itadori	993	131	13.2	102	10.3	6	0.6	23	2.3	Ichiba, 1953
	Shimomaki	1,007	62	6.2	46	4.6	5	0.5	11	1.1	" "
	Kaminoko	682	38	5.6	34	5.0	1	0.1	3	0.4	" "
	Tominoko	412	59	14.3	50	12.1	3	0.7	6	1.5	" "
	Nakayūchi	616	59	9.6	44	7.1	7	1.1	8	1.3	" "
Kumamoto	Kumamoto	1,830	117	6.4	63	3.4	31	1.7	23	1.3	Kida et al., 1949
	Yamaga	2,902	250	8.6	162	5.6	42	1.4	46	1.6	" "
	Kumafu	2,908	275	9.5	175	6.0	48	1.7	52	1.8	" "

TABLE 3—*Concluded*

Prefecture	Village or Town	Number of couples Investigated	Consanguineous marriages		First cousin marriages		1½ Cousin		Second Cousin		Investigator
			#	%	#	%	#	%	#	%	
Kumamoto	Udo	1,092	97	8.9	56	5.1	15	1.4	26	2.4	Kida et al., 1949
	Toride	459	64	13.9	39	8.5	13	2.8	12	2.6	" "
	Hanabusa	390	49	12.6	33	8.5	6	1.5	10	2.6	" "
	Kikuchi	888	124	14.0	84	9.5	14	1.6	26	2.9	" "
	Asahino	416	55	13.2	28	6.7	15	3.6	12	2.9	" "
	Suigen	776	140	18.0	96	12.4	29	3.7	15	1.9	" "
	Higashi Nagashima	1,788	306	17.1	204	11.4	45	2.5	57	3.2	" "
	Nishi Nagashima	1,433	298	20.8	205	14.3	38	2.7	55	3.8	" "
Hiroshima	Kure	8,211	575	7.0	320	3.9	115	1.4	140	1.7	This paper
	Hiroshima	27,934	1,653	5.9	944	3.4	317	1.1	392	1.4	" "
Nagasaki	Nagasaki	33,319	2,667	8.0	1602	4.8	414	1.2	651	2.0	" "
Aichi	Sakushima-mura	437	30	6.9	26	6.0	3	0.7	1	0.2	Kishimoto, 1954
	Nagoya	9,569	251	2.6	205	2.1	10	0.1	36	0.4	" "
Kagawa	Fukuda-mura	629	19	3.0	19	3.0	0	0	0	0	" "

homes, which bears little similarity to that commonly found in rural areas and is more reminiscent of the architecture employed, in the feudal period, in fashioning the homes of the nobility. Be this as it may, of some 28 marriages occurring in this village since 1944, 10 involved first cousins, 5 second cousins, and in the remainder the individuals were more remotely related. More striking, however, are Kida's findings in Gokanosho, an isolated mountain village of over 7000 inhabitants. Here over 40 per cent of the marriages are consanguineous.

Undoubtedly a variety of factors are operating to maintain the high frequency of related marriages in Japan, but certainly two of the more important are the custom of arranged marriages (*baishaku kekkon*) and the family system. The custom and prevalence of arranged marriages is succinctly stated in *Japan: The Official Guide*, a governmental publication, as follows: "Although there are some love marriages and of late years these have been increasingly numerous, most marriages are arranged by friends of the families who act as go-betweens of each party after careful inquiries have been made as to the suitability of the proposed match. There still exists an idea in Japan that marriage is the beginning of love and not the end of it." A number of considerations enter into the arranging of a marriage. Firstly, until such time as a younger son can afford to establish a branch household, or, in the case of an eldest son, until the parents die, the newly married couple will reside with the husband's family. To maintain a home in peace it is essential, then, to select a bride of known disposition, born and reared in an environment relatively similar to that of the groom's family. Secondly, the economic status of each family is of importance. It is generally considered best to arrange a marriage with the families on about equal economic level, or with the girl's family slightly poorer. If there is a marked discrepancy in economic status, with the boy's family the poorer, the bride's family will feel obliged to give their daughter and son-in-law some financial support either directly or indirectly; whereas if the bride's family is markedly poorer, since various

TABLE 4. A SUMMARY OF SOME OF THE REASONS ADVANCED FOR CONSANGUINEOUS MARRIAGES (AFTER ICHIBA, 1953)

Reason	Number
Geographic reasons	40
To settle economic problems	40
Problems of inheritance	4
Prospective mates know each other well	150
He (or she) is the only possible mate	22
No complications involved in arranging a marriage	6
Childhood betrothals	14
Simply repeated the precedent established by parents	8
Requested by will	10
A desire to expand the circle of relatives	34
To maintain peace in the family	8
Other	13
Total	349

gifts are expected at the birth of a child, etc., the bride's family will feel obliged to make an onerous effort to give impressive gifts. In either case, an undue economic hardship is worked on one of the families, and, of course, the other family loses "face." Given these considerations, relatives may become ideal matches.

A further illustration of the value of consanguineous marriage in meeting problems posed by the family system arises in connection with family property. It is customary in Japan, particularly in the rural areas, for family holdings to be used collaboratively by the sons and daughters so long as their father survives. Upon his death, the property is divided among his children and grandchildren, the custom of *sandai no bunkatsu*, the third generation partition. In the past, the eldest son received the lion's share of the family holdings, and the portions received by the other individuals were frequently inadequate to support a family. One effective means of restoring the property to something approaching its former size was for the grandchildren to marry one another.

Some notion of the reasons motivating persons to marry relatives can be obtained from data collected by Ichiba (1953) in the villages of Itadori, Ina, Katagiri, and Okizawa. Each of 349 couples who were related were requested to indicate the principal reason, in their opinion, for related marriages. The results of this inquiry are given in Table 4.[3] It should be noted that the most common reasons advanced for related marriages are geographic, to settle economic problems, and "prospective mates know each other well." We have already commented on the importance, in Japanese eyes, of knowing the graces and foibles of one's mate prior to marriage, and on economic factors favoring consanguineous marriages. The remaining commonly advanced explanation, geographic reasons, does not necessarily imply geographic proximity. In some areas of Japan, *buraku* (hamlet) exogamy is the rule in arranging marriages. Frequently when a young man's marriage is to be arranged in a

[3] Ichiba appears to assume that the answers volunteered by these individuals reflect the motivations in their own marriages. Whether or not this is true is debatable. Responses in circumstances such as this often reflect what is considered culturally desirable rather than individual opinions.

village practicing exogamy, the family is largely compelled to select his mate from relatives since they alone, of the persons living outside the village, would be adequately known to the prospective groom's family.

Let us turn now to a consideration of the attitudes toward consanguineous matches. The official attitude, as revealed by the recent Civil Codes of Japan, is one of forbidding the marriage of relatives of certain specified degrees (under the old code effective until 1947, Article 769; under the present code, Article 734). Thus, the old code, for example, states that "relatives of the direct line, or the collateral relatives within the third degree (aunt-nephew; uncle-niece) cannot marry. But marriage between a *yōshi* and a collateral relative of the adoptive father is excepted." As Nakagawa (1953) has pointed out, this law follows the spirit of similar laws in a number of European countries (e.g., Article 1310, German Civil Code; Article 100, Swiss Civil Code). Interestingly, however, the Japanese code does not specify a penalty associated with the violation of this law, and apparently no effort is made to enforce this article. In Japan, a civil marriage ceremony is not required. One is, however, required to register the fact of marriage with the municipal authorities. At this registration no serious attempt is generally made to ascertain relationship between husband and wife.

The present official attitude is not of recent origin. The Code of a Hundred Articles (*O-Sadame-gaki Hyakkajō*), attributed to Ieyasu Tokugawa but probably written sometime in the 18th Century, observes "One should not live alone after 16 years of age, but should procure a mediator, and perform the ceremony of matrimonial alliance. The same kindred, however, may not intermarry." (Art. XLVI, see Murdoch, 1926, Vol. III, p. 803). An even earlier code, the *Buke-Hatto* (Laws of the Military Houses) promulgated in 1615, asserts "Marriages must not be contracted at private convenience." These laws were directed largely toward the feudal nobility, but even here, they were frequently violated as is apparent on perusal of the *Kansei Chōshū Shō Kafu* (Official Collection of the Genealogies of the *Daimyo*). There is little evidence that these prohibitions were followed by the farmers and artisans.

Among the religious groups in Japan, only the Christian ones place a prohibition on consanguineous marriages (see Schull, 1953). We have been unable to find any restrictions with respect to relationship placed upon marriage by either the Buddhist or Shinto religions. Marriage of relatives is not, however, encouraged by the priests of either religion.

The attitude of the Japanese, in general, toward consanguineous unions has been simply stated in the Japanese Folklore Dictionary (*Minzoku-Jiten*, 1951) as "cousin marriages are even considered desirable." There is, however, a growing awareness of the biologic risks associated with the marriage of relatives. This awareness has been fostered of late by an increasing number of popular articles pointing out the risks (Taniguchi, 1951; Y. Tanaka, 1952; K. Tanaka, 1955). At the same time, there is a continuing tendency to view such marriages as an admissible solution to a variety of problems stemming from the family system prevailing in Japan. Attempts to resolve these two points of view have led to a number of interesting permutations of

marriage practices. Thus, for example, it is commonly held by the less educated Japanese that the father of a child is, in some inexplicable fashion, the more important determiner of the attributes of the child. And from this premise the conclusion is drawn that the risk involved in the marriage of offspring of sisters should be less than in the offspring of brothers. The marriage of the offspring of sisters would, then, more adequately serve the two points of view given above than would the marriage of the offspring of brothers. In a traditionally male-oriented society, such as the Japanese, the initial premise on which this line of reasoning is based is, perhaps, not unexpected. That this common belief may find expression in the choice of a mate seems indicated by data reported by Yanase (1951) and Morton (1955). In a study of the randomness of the four types of first-cousin marriages in Hiroshima, Nagasaki, and Kure in 1948–1952, Morton observed the following in 689 first cousin marriages: 149 involved the offspring of brothers, 229 involved the offspring of sisters, and 311 involved the offspring of a brother and a sister (in 127 cases marriage involved brother's son with sister's daughter). The greatest departure from expectation under an hypothesis of a random distribution of the types of first-cousin marriages is, it will be noted, the increased frequency of the marriage of the offspring of sisters. Whether these figures are typical of Japan is not clear. Embree (1939), on the basis of a study of Suye-mura in Kyushu has asserted that the most common marriage among first cousins involves the offspring of brothers; whereas Beardsley, Hall, and Ward (1958) observed that brother's son with sister's daughter marriages were the most common. These seemingly contradictory results would be reconcilable if the pattern of first-cousin marriages is different among the heads of families from that obtaining among individuals who will establish branch households. In urban areas, branch households would doubtless be relatively more frequent than in rural areas since the founders of branch households are more free to migrate, not being restricted by traditional land holdings.

THE DATA

The circumstances leading to the collection of these data as well as the method by which they were collected have been described *in extenso* elsewhere (Neel and Schull, 1956). Briefly, the data were collected as one facet of a comprehensive attempt to obtain detailed information concerning the various possible late or delayed biological effects of exposure to an atomic bombing. More precisely, the data to be reported arose as a by-product of an attempt to determine whether there can be observed, during the first year of life, any difference between the children born to parents, one or both of whom were exposed to the effects of the atomic bombings of Hiroshima and Nagasaki, and the children born to selected 'control' parents. Since the details of the data collection have been described elsewhere, we shall merely outline the process here, adding certain additional information bearing on the ascertainment of consanguinity.

Prevailing in Japan during the course of this study was a ration system such that pregnant women upon registration of their pregnancy following the completion of the fifth month of gestation could obtain access to certain rationed items. With the assistance of the city administrators of Hiroshima, Nagasaki, and Kure, a system was

instituted whereby, at the time of her registration for ration purposes, each pregnant woman or her representative completed the first two-thirds of a questionnaire which included such items as identifying information, consanguinity, a short summary of the past reproductive performance, and pertinent details concerning the present pregnancy. This questionnaire, which was administered by trained clerks, was filled out in duplicate; the original was given the registrant, while the Atomic Bomb Casualty Commission, the agency charged with ascertaining the delayed effects of the atomic bombing, retained the copy. At the termination of the pregnancy, the midwife or physician in attendance completed the questionnaire by answering certain questions pertaining to the characteristics of the child and delivery, and notified the Commission of the termination of the pregnancy. Irrespective of the outcome of the pregnancy, a Japanese physician in the employ of the Commission or the Japanese National Institute of Health called to examine the child. Through the attendant at birth and/or the examining physician, information was obtained on the sex, birthweight, and presence of malformation in the child as well as whether the child was live or stillborn, and if liveborn, whether death occurred in the first month of life. The Commission's physician in addition to examining the child verified certain items of information obtained at the time of registration. While the bulk of these items had to do with identification of the pregnancy, included among them was the occurrence of consanguinity.

If upon examination the child was found to be abnormal, in the sense that the child possessed a major congenital malformation, was stillborn, or died during the neonatal period, a more-detailed questionnaire was completed by the examining physician. While the primary purpose of this questionnaire was to obtain more-detailed information on the abnormality, information was also collected with respect to the occurrence of defect in the mother's or father's family, gynecologic history, maternal disease during pregnancy, past reproductive performance, and economic status. In addition, blood was drawn from the mother for a serologic test for the presence of syphilis. This same procedure was followed routinely on every pregnancy where the registration number, assigned in sequence at the time of registration, terminated in zero.

Two additional sources of data require brief mention here. Firstly, a concerted attempt was made, particularly in Hiroshima, to obtain for necropsy the bodies of infants who were stillborn or died in the first seven days of life. In Hiroshima and Nagasaki combined, 89 infants born to related parents came to necropsy; of this number, 60 were the offspring of registered parents. Secondly, in 1950, there was inaugurated a program to reexamine, at the age of 9 months, the children examined shortly after birth. The number of these reexaminations was determined by the available clinical facilities. To obtain a sample, selection of the infants to be seen was by the terminal registration digit of the pregnancy. In the event that it was not possible to examine a child, who was included in the sample, an effort was made to establish why, in an attempt to detect possible sources of bias. Of the total infants selected for examination, in about five per cent of cases the parents had moved from the city some time after the birth of the infant selected, and in slightly less than one per cent of cases the child was not seen for a variety of other reasons, including the refusal

of the parents to have the child examined, and illness in the family at the time of the scheduled clinic visit. There is no indication in these data that failures to examine children selected for study were more frequent when the parents were unrelated than when they were related. The purposes of this second examination were several-fold. It afforded a check on diagnostic oversights at the first examination and an opportunity for supplemental diagnoses. It permitted extension of the distribution of infant deaths from one week to 9 months of age. Finally, it presented an occasion to appraise the mental and physical growth and development of these children not otherwise possible.

In addition to the verification of consanguinity by the examining physician to which we have previously alluded, verification was routine whenever the mother registered for a subsequent pregnancy (approximately one-fourth of the mothers registered more than once during the course of the study). In the event of a discrepancy in responses, a further attempt to verify the information was made by sending a trained interviewer to interview the mother. In a sample of more than 6000 consecutive registrations, 16 corrections of consanguinity information were made by the examining physician, and 14 through verification of a previous registration; among the latter, in six instances the verified information differed from both registrations. Collectively, there were 15 instances of consanguinity not ascertained at registration, and 14 changes in degree of consanguinity. No instance of denial of previously reported consanguinity was recorded. In general, an effort was made to uncover all relationships up to and including second cousins. If the individuals knew of more remote relationship, this was recorded; however, no special attempt was made to probe for distant relationships. It must be clearly recognized, therefore, that there exists within these data some unrecognized inbreeding (we shall indicate later the probable magnitude of this covert inbreeding), and that "unrelated" parents are merely individuals reporting themselves to be unrelated. We may safely assume that if some of the latter individuals are, in fact, related, it is unlikely that they are more closely related than second cousins.

To determine more accurately the reliability of the consanguinity information, Japanese physicians in the employ of the ABCC carefully verified 768 registrations by revisiting the mother. The sample chosen for verification consisted of parents reported to be first cousins, first cousins once removed, or second cousins, whose registration numbers ended in 1 or 6. The sample was so chosen for two reasons. Firstly, since corrections of degree of relationship were almost as frequent as corrections in fact of consanguinity, despite the fact that consanguinity occurs in less than 10 per cent of the marriages here recorded, it seemed clear that determination of degree of consanguinity was the weakest part of the data. Secondly, it was the impression of the various interviewers that Japanese parents were well informed of consanguinity between husband and wife and not indisposed to discuss their relationship, but that degree of consanguinity was sometimes poorly ascertained by the interviewer. The results of this special verification study are presented in Table 5. It will be noted that the consanguinity information is not without error despite the several checks to which it was subjected. One common source of error was the failure to record the details of multiple relationships or relationship through a single common ancestor

TABLE 5. RELIABILITY OF THE CONSANGUINITY DATA AS JUDGED BY SPECIAL VERIFICATION OF A SAMPLE OF REPORTEDLY RELATED PARENTS

Previous record of parental relationship	Verified record of parental relationship							F	
	First cousins	1½ cousins	Second cousins	Remote, degree uncertain	Not related	Other	Total	Obs.	Exp.
First cousins	433	3	7	1	4	15	463	.0604	.0625
1½ cousins	1	95	6	—	2	6	110	.0311	.0313
Second cousins	4	14	155	5	4	13	195	.0171	.0156
Total	438	112	168	6	10	34	768		

(half cousins, etc.). Ten of the parents were not related by blood; of these, 2 were related by adoption, 3 by marriage, 3 by a previous marriage, for 1 case no details were given, and in 1 case there was an error in coding. In the entire sample, 683 cases appear to have been correctly ascertained, and among the remainder, the errors are distributed such that the "observed" inbreeding coefficient is, for each degree of relationship, nearly identical with its theoretical value. Because of this cancellation of errors, the consanguinity data are considerably more reliable than might be supposed from the frequency of corrections alone, and random errors can probably be neglected. The author is unaware of any other consanguinity study in which an attempt has been made to determine the reliability of responses in a manner similar to that here presented. It is not possible, therefore, to form an opinion as to whether the errors in ascertaining consanguinity in Japan are greater or less than usual.

We shall in the ensuing sections restrict our attentions to those registered pregnancy terminations where neither parent sustained exposures to nuclear energy exceeding class 2 (estimated mean dose 5 reps; see Neel and Schull, 1956). By so restricting the data there is little possibility of confounding radiation and inbreeding effects. In this connection, it is perhaps worth pointing out that in some 60 per cent of the cases to follow neither parent was exposed.

In addition to the rejection of certain pregnancy terminations on the basis of parental exposure to the atomic bombings, a pregnancy termination was rejected if (1) the termination was induced and the birth weight of the infant was less than 2,500 grams, (2) the birth weight was not recorded, (3) the birth rank (parity) was not recorded, (4) the gestation was less than 21 weeks, or unknown and the infant weighed less than 2,500 grams, (5) the sex of the infant was not recorded, or (6) the age of the mother was unknown. A justification of these various bases for rejection is to be found in Neel and Schull (1956). Two differences between the present study and that of Neel and Schull in cases which were rejected are the inclusion, here, of diagnoses of congenital heart disease, and the infants seen at nine months of age on whom an incomplete set of anthropometric measurements was obtained.

THE COMPARABILITY OF THE SUBCLASSES OF RELATIONSHIP

In this section as well as in the sections to follow, in considering relationship, we shall restrict ourselves to four groups, namely, unrelated parents, first cousins, first cousins once removed (1½ cousins), and second cousins. A few uncle-niece and some unions of more remote relationship than second cousins were enumerated. These

two groups have been excluded for two reasons. Firstly, the numbers are too small to analyze with much profit, and secondly, it is certain that relationships more remote than second cousins were not exhaustively ascertained.

As has been indicated, the data are drawn from three cities, Kure, Hiroshima and Nagasaki. A brief description of the nature of Hiroshima and Nagasaki will be found in Neel and Schull (1956). Kure is a city of rather recent origin stemming primarily from the establishment of the Kure Naval Yards in June, 1889. As these yards grew—by 1940 they were the largest naval yards in Japan—they dominated the economic life of the city. Until the end of World War II, the development of Kure was largely determined by what best served the interests of the Japanese Navy. In the post-war period, Kure has been a major center of the forces occupying Japan. Thus, at no time in its existence has Kure been a "typical" Japanese city. The data collected in Kure were obtained in the years 1948–1950 when it was uncertain whether Hiroshima would rebuild rapidly enough to provide an adequate internal control for the radiation studies. As soon as it became apparent that an adequate control could be obtained in Hiroshima, the studies in Kure were terminated.

These three cities and the subclasses of relationship differ in a number of important respects to which we now turn our attention. Table 6 presents the distribution of the

TABLE 6. THE DISTRIBUTION OF PARENTAL RELATIONSHIPS AMONG REGISTERED INFANTS BORN IN HIROSHIMA, KURE, AND NAGASAKI IN THE YEARS 1948–1954

City	Parental relationship							Total
	Unrelated	First Cousins		1½ Cousins		Second Cousins		
	n	n	p	n	p	n	p	
Hiroshima:								
1948	2,704	117	.0402	40	.0137	50	.0172	2,911
1949	5,959	208	.0329	65	.0103	91	.0144	6,323
1950	5,153	220	.0399	75	.0136	67	.0121	5,515
1951	4,604	178	.0362	53	.0108	83	.0169	4,918
1952	4,088	125	.0290	41	.0095	52	.0121	4,306
1953	3,744	93	.0237	43	.0109	49	.0125	3,929
1954	29	3		—		—		32
Total	26,281	944	.0338	317	.0113	392	.0140	27,934
Kure:								
1948	1,626	84	.0473	27	.0152	39	.0220	1,776
1949	4,175	141	.0317	65	.0146	71	.0159	4,452
1950	1,835	95	.0479	23	.0116	30	.0151	1,983
Total	7,636	320	.0390	115	.0140	140	.0171	8,211
Nagasaki:								
1948	648	38	.0534	10	.0140	16	.0225	712
1949	7,385	422	.0523	95	.0118	163	.0202	8,065
1950	6,410	353	.0504	91	.0130	149	.0213	7,003
1951	6,008	300	.0461	81	.0125	116	.0178	6,505
1952	5,580	292	.0481	79	.0130	117	.0193	6,068
1953	4,573	197	.0401	57	.0116	90	.0183	4,917
1954	48	—		1		—		49
Total	30,652	1,602	.0481	414	.0124	651	.0195	33,319
Total	64,569	2,866	.0413	846	.0122	1,183	.0170	69,464

four classes of relationship by city and year of registration of the infant. In all three cities, the initial and terminal years recorded are incomplete due to either the initiation or termination of observations at some date other than January 1. The frequencies of consanguineous marriages in these data lead to average coefficients of inbreeding (α) of 0.00269 (Hiroshima), 0.00314 (Kure), and 0.00370 (Nagasaki). Since consanguineous marriages in Japan have undoubtedly been more common in the past, and since these coefficients are computed on the assumption that the common ancestors were themselves not inbred, these values unquestionably underestimate the true coefficients of inbreeding. It is difficult to determine to what extent these are underestimates; however, from data collected by Nagashima (1949) on red-green colorblindness on the island Sado (in the Japan Sea near the city of Niigata), one can estimate that the true inbreeding coefficients may be as much as one-third higher. To arrive at this correction requires, of course, certain assumptions regarding the frequency with which heterozygous females exhibit red-green colorblindness, and randomness of cousin matings.

Inspection of Table 6 reveals several items of interest. Firstly, Hiroshima and Nagasaki clearly exhibit temporal trends, the proportion of births to related parents diminishing with time. Secondly, "total" consanguinity, here defined as the proportion of all infants born to parents related as first cousins, first cousins once removed, or second cousins, differs significantly between cities ($\chi^2 = 101.058$, DF = 2). Lastly, the proportion of first cousin marriages among all related marriages differs between cities, not significantly but nearly so ($\chi^2 = 5.936$, DF = 2). The totals in subsequent tables will differ somewhat from those in Table 6 due to the exclusion of multiple births. In this connection, it can be shown that the frequency of multiple births does not differ significantly nor appreciably among the classes of relationship.

There exist reasons for suspecting that individuals who contract marriages with relatives may differ with respect to a number of socio-economic factors from those individuals who are unrelated to their spouses. Available to test this thesis are data on maternal age at the termination of the registered pregnancy, number of conceptions of a given mother, the economic status of the parents, the frequency of positive serology among parturient mothers, and the age differential between husband and wife. There follows a brief consideration of the distributions of these socio-economic concomitants of marriage among the classes of parental relationship.

In Tables 7 and 8 are presented data on economic status and frequency of positive serological tests for syphilis among parturient mothers by city and parental relationship. In any appraisal of the data with regard to economic status, the following should be borne in mind: The determination of economic status was a value judgment by a physician in the employ of ABCC or the Japanese National Institute of Health made at the time of the home visit examination of the child. Each family was assigned to one of five economic classes, namely, very poor, poor, average, well-to-do, and rich. The roughness of this scheme is apparent; however, since in the course of time each physician found himself in all sections of a city, among all economic classes, and among all classes of parental relationship, it seems likely that even this rough classification would detect any marked difference among related classes within a city. The subjectivity of the classification makes it difficult, however, to evaluate the reality

TABLE 7. THE DISTRIBUTION OF ECONOMIC STATUSES BY CITY AND PARENTAL RELATIONSHIP

City	Economic status	Parental relationship			
		First Cousins	1½ Cousins	Second Cousins	Unrelated
Hiroshima	Below	32	12	17	751
	Average	317	115	134	6,917
	Above	12	3	5	435
Kure	Below	5	1	3	162
	Average	66	26	36	1,525
	Above	5	1	1	108
Nagasaki	Below	54	17	24	1,175
	Average	284	68	114	5,315
	Above	17	4	10	342

Source	χ^2	DF	P
Hiroshima	7.054	6	.25–.50
Kure	3.298	6	.75–.90
Nagasaki	2.251	6	.75–.90

TABLE 8. THE DISTRIBUTION OF POSITIVE SEROLOGICAL TESTS FOR SYPHILIS BY CITY AND RELATIONSHIP OF MOTHER TO HER SPOUSE. THE NUMBER OF MOTHERS WITH POSITIVE SEROLOGICAL TESTS FOR SYPHILIS IS INDICATED BY +

City		Parental Relationship				Total
		First Cousins	1½ Cousins	Second Cousins	Unrelated	
Hiroshima	n	350	126	152	7,659	8,287
	+	12	4	2	278	296
	p	.0343	.0317	.0132	.0363	.0357
Kure	n	67	25	35	1,623	1,750
	+	4	—	2	89	95
	p	.0597	—	.0571	.0548	.0543
Nagasaki	n	342	90	144	6,476	7,052
	+	9	5	12	410	436
	p	.0263	.0556	.0833	.0633	.0618
Total	n	759	241	331	15,758	17,089
	+	25	9	16	777	827
	p	.0329	.0373	.0483	.0493	.0484

Source	χ^2	DF	P
Hiroshima	2.399	3	.50–.30
Kure	0.561	2	.80–.70
Nagasaki	8.890	3	.05–.02

of the city differences. The discrepancy in total number of observations between Tables 7 and 8 is due to the exclusion from the latter table of those mothers who were not tested serologically or who gave doubtful serological reactions.

From Table 7, it is apparent that while the cities differ appreciably, there is no evidence that the distribution of economic statuses is markedly different among the

classes of parental relationship within a city. In Table 8, the frequency of mothers exhibiting positive serological tests for syphilis is distributed by city and parental relationship. Again, while there are significant differences between cities reflecting socio-economic differences, undoubtedly, there is no evidence that classes of parental relationship differ in the frequency of mothers with positive serological tests. It should be pointed out, however, that a significant negative association between coefficient of inbreeding and frequency of positive serological tests for syphilis can be demonstrated when one disregards the city classification. This does not, however, appear to be an especially meaningful test in view of (1) the demonstrable differences between cities and the disproportionate contribution of the cities to the consanguinity totals, and (2) one cannot demonstrate a significant association when allowance is made for different city intercepts.

In Tables 9 and 10 are given the means and variances for maternal age and parity by city and parental relationship. Here and elsewhere ages have been recorded in the Occidental fashion and to the nearest year. To allow for the disproportionate numbers of observations in the various city-consanguinity cells, analysis of the means has been by the "method of fitting constants". The model on which the main effects were estimated was a "no interaction model". If a significant interaction exists, the main-effects tests are only approximations since they confound interaction (when the within-cells mean square is used as the error variance). In the analysis of the

TABLE 9. MEANS AND VARIANCES FOR MATERNAL AGE BY CITY AND PARENTAL RELATIONSHIP

Parental Relationship		Hiroshima	Kure	Nagasaki
First cousins	$\bar{x}$	27.07	28.10	28.44
	s^2	22.50	31.10	29.78
	n	936	318	1,592
First cousins once removed	$\bar{x}$	26.86	28.12	27.95
	s^2	24.26	24.00	28.69
	n	313	113	412
Second cousins	$\bar{x}$	27.26	27.79	27.80
	s^2	25.09	34.52	24.82
	n	384	140	637
Unrelated	$\bar{x}$	27.24	27.92	28.60
	s^2	23.47	31.14	29.68
	n	26,012	7,544	30,240

Homogeneity of the means

Source of Variation	Sum of Squares	DF	Mean Square	F
Cities	27,114	2	13,557	496.59**
Relationship	424	3	141	5.16**
Interaction	269	6	45	1.65
Between classes	27,654	11	2,514	92.09**
Within classes	1,873,451	68,629	27.30	
Total	1,901,105	68,640		

Homogeneity of the variances

Bartlett's test $\chi^2 = 497.00^{**}$ DF = 11

TABLE 10. MEANS AND VARIANCES FOR PARITY BY CITY AND PARENTAL RELATIONSHIP

Parental Relationship		Hiroshima	Kure	Nagasaki
First cousins	$\bar{p}$	2.74	2.97	3.25
	s^2	2.50	3.46	4.13
	n	936	318	1,592
First cousins once removed	$\bar{p}$	2.85	3.04	3.18
	s^2	2.81	2.97	3.72
	n	313	113	412
Second cousins	$\bar{p}$	2.73	2.96	3.04
	s^2	3.29	3.45	3.37
	n	384	140	637
Unrelated	$\bar{p}$	2.51	2.71	3.01
	s^2	2.40	3.31	3.46
	n	26,012	7,544	30,240

Homogeneity of the means

Source of Variation	Sum of Squares	DF	Mean Square	F
Cities	3,683	2	1,842	605.92**
Relationship	223	3	74	24.34**
Interaction	73	6	12	3.95**
Between classes	3,996	11	363	119.41**
Within classes	208,774	68,629	3.04	
Total	212,770	68,640		

Homogeneity of the variances

Bartlett's test $\chi^2 = 1{,}078.34^{**}$ DF = 11

concomitant variables, our purpose is not to pursue the effects of these variables, *per se*, but rather to determine whether the various city-consanguinity cells are heterogeneous. Since heterogeneity is established by either a significant interaction or a main effect, we shall not, in the presence of a significant interaction, be concerned about the "best" test of the main effects. In both tables, we note that not only do the means differ significantly between cities but also among classes of parental relationship. Moreover, in the case of parity (or birth rank), the effect of consanguinity is not independent of city effect. In general, mothers who are related to their husbands are younger and have had more pregnancies than those mothers who are unrelated to their husbands. We further note significant differences between city-consanguinity classes with respect to the variances for maternal age and parity. Variation in age of mother exhibits no clear trend with respect to parental relationship, whereas, in the main, there is greater variation in number of pregnancies among related than among the unrelated parents. It can be shown that among these data the proportion of related parents who are of rural origin among all related parents is greater than the proportion of unrelated parents who are of rural origin among all unrelated parents. Since marriages occur somewhat earlier in rural than in urban areas, this may account for the observed differences in mean maternal age and mean number of pregnancies. The occurrence of these differences among classes of parental relationship, whatever their origin, further complicates efforts to dissociate effects of inbreeding from the known effects of maternal age and parity.

To complete the picture of the age stratification of the classes of relationship we present in Tables 11–13 the (1) means and variances for age of father by city and consanguinity, (2) the correlation in age between spouses, and mean differences between mother's age and father's age, and (3) mean age differences among the four types of first-cousin marriages for a sample of approximately 100 marriages of each type. It will be noted that the fathers tend to be younger when related to their spouses although the differences are less striking than for maternal age. Moreover,

TABLE 11. MEANS AND VARIANCES FOR FATHER'S AGE BY CITY AND RELATIONSHIP TO SPOUSE

City		Parental Relationship			
		First Cousins	1½ Cousins	Second Cousins	Unrelated
Hiroshima	$\bar{x}$	32.27	32.18	32.59	32.77
	s^2	31.84	32.95	34.25	39.51
Kure	$\bar{x}$	32.75	33.10	33.10	33.36
	s^2	37.21	35.29	41.66	44.91
Nagasaki	$\bar{x}$	33.28	34.20	32.95	33.85
	s^2	39.39	40.47	34.79	46.30

TABLE 12. THE DISTRIBUTION OF THE MEAN DIFFERENCES BETWEEN MOTHER'S AND FATHER'S AGES AND THE CORRELATION BETWEEN THESE AGES BY CITY AND PARENTAL RELATIONSHIP

City		Parental Relationship			
		First Cousins	1½ Cousins	Second Cousins	Unrelated
Hiroshima	$\bar{x}$	4.68	4.74	4.87	5.04
	s^2	16.39	13.20	15.85	18.16
	r	0.69	0.75	0.72	0.70
Kure	$\bar{x}$	4.18	4.27	4.02	5.00
	s^2	13.38	11.85	13.27	16.92
	r	0.80	0.81	0.82	0.77
Nagasaki	$\bar{x}$	4.31	5.73	4.51	4.74
	s^2	15.23	15.40	14.43	18.79
	r	0.77	0.79	0.74	0.75

TABLE 13. AGE DIFFERENCES BETWEEN SPOUSES IN THE VARIOUS TYPES OF FIRST-COUSIN MARRIAGES

	Type of first-cousin marriage			
	Bro-Bro	Sis-Sis	BroSo-SisDa	BroDa SisSo
n	104	128	103	115
Mean	4.47	4.28	4.61	4.97
Variance	16.83	12.77	12.08	12.44
Correlation	0.77	0.80	0.76	0.79

Bro-Bro = offspring of brothers
Sis-Sis = offspring of sisters
BroSo-SisDa = brother's son and sister's daughter
BroDa-SisSo = brother's daughter and sister's son

the distributions of fathers' ages are less variable when relationship to the spouse exists than when no relationship exists. The correlation in age between husband and wife tends to be higher when the husband and wife are related although the differences are less marked than the differences between cities within a consanguinity class. Lastly, the mean age differences between spouses for the various types of first-cousin marriages are not significantly different nor, for that matter, are the variance estimates. It is interesting to observe, however, that the average differences in age are greater for cross cousins than for parallel cousins and that less variation of the difference in the age of the spouses exists when they are cross cousins. The age differences reported here are in substantial agreement with those obtained by Ichiba (1953) in a study of consanguineous marriages in four villages in Gifu, Nagano, and Fukushima Prefectures. Ichiba also finds that husband and wife tend to be younger when related and that the difference in ages between spouses is less, being 3.64 years when related and 4.90 years when unrelated.

One other possible difference among classes of parental relationship requires comment, and this is the frequency with which mothers in the various classes have had pregnancies therapeutically interrupted. In the post-war years, Japan, in an effort to control the growth of her population, has relaxed the indications for legal "therapeutic" abortion. At the present time, a pregnancy can be interrupted on any one or combination of three grounds, namely, the pregnancy constitutes a threat to the mother's health, economic distress would result from further children, or there is reason to suspect that the pregnancy may terminate in a child who for one reason or another would be deemed to be an unwelcome addition to society (for more on the

TABLE 14. THE FREQUENCY OF MOTHERS REPORTING ONE OR MORE INDUCED ABORTIONS AT THEIR FIRST REGISTRATION BY CITY AND RELATIONSHIP TO SPOUSE

City		Parental relationship				Total
		First Cousins	1½ Cousins	Second Cousins	Unrelated	
Hiroshima	n	625	215	274	17,922	19,036
	t	22	10	19	945	996
	p	.0352	.0465	.0693	.0527	,0523
Kure	n	239	87	101	5,969	6,396
	t	1	2	—	52	55
	p	.0042	.0230	—	.0087	.0086
Nagasaki	n	1,074	274	426	20,848	22,622
	t	12	4	3	450	469
	p	.0112	.0146	.0070	.0216	.0207
Total	n	1,938	576	801	44,739	48,054
	t	35	16	22	1,447	1,520
	p	.0181	.0278	.0275	.0323	.0316

Source	χ^2	DF	P
Cities	464.558	2	<.001
Consanguinity	13.127	3	<.01
Interaction	2.602	6	.75–.90
Total	480.286	11	<.001

eugenic aspects see Komai, 1957). In point of fact, the law is sufficiently liberal that the only deterrents to a legal interruption of a pregnancy are the cost and the feeling, held by many, that therapeutic abortions are contrary to family tradition and the natural order of things. Therapeutic interruption of a pregnancy in Japan generally takes the form of dilatation and curettage of the uterus sometime within the first three months of gestation. Conceivably uterine infection and cicatrization following an induced abortion may influence subsequent pregnancy terminations. For this reason, it has seemed advisable to investigate the distribution by parental relationship of mothers reporting one or more therapeutic abortions prior to the pregnancy which led to their registration. These data are presented in Table 14. Significantly fewer induced abortions have occurred to related parents. The significant differences between cities undoubtedly rest on several factors. The lower rate in Kure reflects, without doubt, the fact that the collection of data was terminated not long after the present laws with respect to therapeutic abortions were promulgated, and hence before many women could avail themselves of the new regulations. The low rate in Nagasaki is more difficult to account for but presumably some of the difference between Nagasaki and Hiroshima is attributable to the sizable Roman Catholic population in Nagasaki not present in Hiroshima. The position of the Catholic Church with regard to abortion is well known.

THE INFLUENCE OF CONSANGUINITY ON THE EFFECTS OF MATERNAL AGE AND PARITY ON PREGNANCY OUTCOME

There exists an extensive literature attesting to the effect of maternal age and parity on pregnancy outcome. Moreover, we have presented elsewhere (Neel and Schull, 1956) evidence that maternal age and/or parity exert a measurable effect on the frequencies of congenital malformations, stillbirths, neonatal deaths, and on birthweight, among infants born in Japan. We ask, now, "Are the effects of maternal age and parity on pregnancy outcome altered by parental relationship?" In view of the demonstrated differences in maternal age and parity among the classes of parental relationship, upon the answer to this question hinges the form of the analysis of the data on pregnancy terminations.

Table 15 presents the distribution of total births and infants congenitally malformed by mother's age and parity for the four classes of parental relationship (cities are pooled). In Table 16 is given the distribution (by maternal age, parity, and relationship) of all infants not known to be malformed and the numbers of such infants who were stillborn or who died in the first seven days of life. It seems unlikely that the combining of stillborn infants with those dying in the first seven days of life will lead to the loss of significant information with respect to maternal age and parity effects. This belief rests on the observations of Yerushalmy (1938, 1945), and Neel and Schull (1956) who found that the general effects of maternal age and parity appear to be the same for stillbirths as for neonatal deaths. Furthermore, since the bulk of deaths occurring in the first seven days of life actually occur in the first twenty-four hours following delivery, before exogenous factors can exert much influence, it seems reasonable to assume that some of the factors contributing to the occurrence of stillbirths also contribute to death in the first seven days of life.

TABLE 15. THE DISTRIBUTION OF MALFORMED INFANTS BY CONSANGUINITY, MATERNAL AGE, AND PARITY

	Mat. Age	1		2		3		4		5		6		7		8		9		10		Total	
		n	m	n	m	n	m	n	m	n	m	n	m	n	m	n	m	n	m	n	m	n	m
Unrelated	15–19	1044	5	155	1	10	0	4	0	—	—	—	—	—	—	—	—	—	—	—	—	1213	6
	20–24	9630	87	5822	64	1474	12	272	2	51	0	10	0	1	0	—	—	—	—	—	—	17260	165
	25–29	4962	37	8538	74	6449	67	2645	29	767	8	152	3	30	0	6	1	—	—	1	0	23550	219
	30–34	1000	10	2231	22	3530	46	3300	21	2056	33	975	14	302	3	87	1	18	0	13	0	13512	150
	35–39	282	3	535	5	869	9	1145	15	1260	15	1078	14	705	6	336	4	151	1	94	1	6455	73
	40–44	47	1	95	1	121	3	169	4	193	5	291	8	277	3	222	7	172	3	151	3	1738	38
	45+	—	—	1	0	4	0	6	0	7	0	12	0	9	0	10	0	6	0	13	0	68	0
	Total	16965	143	17377	167	12457	137	7541	71	4334	61	2518	39	1324	12	661	13	347	4	272	4	63796	651
First Cousins	15–19	44	0	8	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	52	2
	20–24	351	6	299	2	89	0	14	0	3	0	—	—	—	—	—	—	—	—	—	—	756	8
	25–29	167	4	376	6	323	5	152	1	52	2	14	0	3	0	1	0	3	0	—	—	1088	18
	30–34	25	0	81	1	127	4	146	1	111	5	57	1	24	1	7	0	—	—	—	—	581	13
	35–39	6	0	13	0	26	0	30	0	69	2	49	3	41	1	26	1	15	0	9	0	284	7
	40–44	—	—	4	0	3	0	4	0	11	0	9	0	21	0	13	0	4	0	9	0	78	0
	45+	—	—	—	—	—	—	1	0	1	0	—	—	—	—	2	0	2	0	1	0	7	0
	Total	593	10	781	11	568	9	347	2	247	9	129	4	89	2	49	1	24	0	19	0	2846	48
1½ Cousins	15–19	13	0	2	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	15	1
	20–24	105	1	109	1	37	1	5	0	—	—	—	—	—	—	—	—	—	—	—	—	256	3
	25–29	36	0	89	1	100	1	48	0	18	0	5	0	—	—	—	—	—	—	—	—	296	2
	30–34	4	0	26	0	42	0	47	0	33	0	12	1	4	0	4	0	—	—	—	—	172	1
	35–39	2	0	3	0	4	0	15	0	19	1	21	0	6	0	4	0	3	0	4	0	81	1
	40–44	—	—	—	—	—	—	—	—	1	0	3	0	6	0	2	0	1	0	4	0	17	0
	45+	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	0	1	0
	Total	160	1	229	3	183	2	115	0	71	1	41	1	16	0	10	0	4	0	9	0	838	8
Second Cousins	15–19	25	0	1	0	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	26	0
	20–24	162	2	134	0	33	1	3	0	1	0	2	0	—	—	—	—	—	—	—	—	335	3
	25–29	64	1	161	3	130	1	53	2	17	0	4	0	1	0	—	—	—	—	—	—	430	7
	30–34	9	0	22	0	58	1	67	1	42	0	22	0	8	0	1	0	2	0	1	0	232	3
	35–39	4	0	4	0	8	0	20	0	25	0	21	0	17	0	8	0	2	0	5	0	114	0
	40–44	—	—	3	0	2	0	2	0	1	0	3	0	1	0	4	0	6	0	2	0	24	0
	45+	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Total	264	3	325	3	231	3	145	3	86	1	52	0	27	0	13	0	10	0	8	0	1161	13

TABLE 16. THE DISTRIBUTION OF STILLBIRTHS AND NEONATAL DEATHS AMONG INFANTS WITHOUT VISIBLE GROSS MALFORMATION BY CONSANGUINITY, MATERNAL AGE, AND PARITY

	Mat. Age	1		2		3		4		5		6		7		8		9		10		Total	
		n	d	n	d	n	d	n	d	n	d	n	d	n	d	n	d	n	d	n	d	n	d
Unrelated	15–19	1039	33	154	3	10	0	4	0	—	—	—	—	—	—	—	—	—	—	—	—	1207	36
	20–24	9543	298	5758	144	1462	40	270	10	51	6	10	2	1	1	—	—	—	—	—	—	17095	501
	25–29	4925	193	8464	187	6382	156	2616	66	759	29	149	6	30	1	5	1	—	—	1	0	23331	639
	30–34	990	50	2209	49	3484	84	3279	74	2023	44	961	23	299	12	86	2	18	1	13	1	13362	340
	35–39	279	23	530	19	860	26	1130	38	1245	31	1064	22	699	27	332	9	150	5	93	9	6382	209
	40–44	46	5	94	3	118	2	165	2	188	7	283	14	274	14	215	7	169	6	148	6	1700	66
	45+	—	—	1	0	4	0	6	0	7	1	12	3	9	0	10	1	6	1	13	1	68	7
	Total	16822	602	17210	405	12320	308	7470	190	4273	118	2479	70	1312	55	648	20	343	13	268	17	63145	1798
First Cousins	15–19	44	3	6	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	50	4
	20–24	345	14	297	11	89	5	14	1	3	0	—	—	—	—	—	—	—	—	—	—	748	31
	25–29	163	4	370	8	318	10	151	7	50	2	14	2	3	0	1	0	—	—	—	—	1070	33
	30–34	25	0	80	3	123	5	145	5	106	3	56	0	23	1	7	2	3	0	—	—	568	19
	35–39	6	1	13	2	26	1	30	1	67	1	46	1	40	0	25	2	15	2	9	0	277	11
	40–44	—	—	4	1	3	0	4	0	11	0	9	0	21	1	13	0	4	0	9	0	78	2
	45+	—	—	—	—	—	—	1	0	1	0	—	—	—	—	2	0	2	0	1	0	7	0
	Total	583	22	770	26	559	21	345	14	238	6	125	3	87	2	48	4	24	2	19	0	2798	100
1½ Cousins	15–19	13	1	1	0	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	14	1
	20–24	104	5	108	3	36	2	5	0	—	—	—	—	—	—	—	—	—	—	—	—	253	10
	25–29	36	2	88	1	99	5	48	0	18	0	5	0	—	—	—	—	—	—	—	—	294	8
	30–34	4	0	26	2	42	1	47	0	33	0	11	0	4	0	4	0	—	—	—	—	171	3
	35–39	2	0	3	0	4	0	15	0	18	0	21	0	6	0	4	0	3	0	4	0	80	0
	40–44	—	—	—	—	—	—	—	—	1	0	3	0	6	0	2	0	1	0	4	0	17	0
	45+	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	0	1	0
	Total	159	8	226	6	181	8	115	0	70	0	40	0	16	0	10	0	4	0	9	0	830	22
Second Cousins	15–19	25	1	1	0	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	26	1
	20–24	160	3	134	1	32	2	3	0	1	0	2	0	—	—	—	—	—	—	—	—	332	6
	25–29	63	3	158	4	129	4	51	1	17	2	4	0	1	0	—	—	—	—	—	—	423	14
	30–34	9	0	22	0	57	3	66	5	41	1	22	0	8	1	1	0	2	0	1	0	229	10
	35–39	4	0	4	0	8	0	20	2	25	1	21	1	17	1	8	0	2	0	5	0	114	5
	40–44	—	—	3	0	2	0	2	0	1	0	3	0	1	0	4	0	6	2	2	0	24	2
	45+	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Total	261	7	322	5	228	9	142	8	85	4	52	1	27	2	13	0	10	2	8	0	1148	38

As is apparent from Tables 15 and 16, the data are not sufficient to allow sophisticated treatment of the influence of consanguinity on the effects of maternal age and parity on the occurrence of congenital malformations or perinatal deaths, that is, death during parturition or in the first seven days thereafter. However, since it is unlikely that a larger body of data than these will be immediately forthcoming, it would seem appropriate to explore, in at least a preliminary fashion, the question of the association of maternal age and parity effects with consanguinity.

Figures 1–3 relate the frequency of abnormal pregnancy terminations with maternal age, parity, and parity for specified maternal age. To obtain a greater measure of stability in the variable, we have resorted to two devices, namely, the combination of (1) perinatal deaths and congenital malformations as abnormal pregnancy terminations, and the combination of (2) terminations occurring to first cousins once removed and to second cousins. Two features of these data warrant singling out for comment. Firstly, at all ages, or parities where the numbers of terminations are fairly large, there occur more abnormal terminations among the pregnancies of first cousins than among those of unrelated individuals. The frequency of abnormal terminations among "first cousins once-removed and second cousins" is more or less intermediate between the unrelated and first-cousin groups. Secondly, the general shape of the maternal age or parity curves is surprisingly similar for first cousins and unrelated parents. Greater instability is shown in the combined first-cousins-once-removed and second-cousin group; however, the values for this latter group tend to fluctuate between the other two groups. It would appear that if consanguinity exerts any influence on the effects of maternal age and parity the effect is small.

It may be argued that combining congenital malformations with perinatal deaths when the effects of maternal age and parity are not the same, or at least do not appear to be the same, would obfuscate an association of consanguinity with maternal age and parity effects. In this connection, it is worth noting that the curves for perinatal deaths alone though exhibiting greater instability are substantially the same as Figures 1–3. Moreover, since the ratio of perinatal deaths to congenital malformations is reasonably constant over the classes of parental relationship, it seems reasonable to assume that whatever distortion may arise from pooling would be proportional.

We have presented elsewhere (Neel and Schull, 1956) evidence that among the offspring of unrelated parents the effects of maternal age and parity on birthweight, as measured in tens of grams, can be adequately approximated by a regression of the form

$$\hat{y} = m + b_1x + b_2w + b_3z$$

where

$\hat{y}$ = birthweight
m = mean birthweight
x = parity
w = parity squared
z = maternal age

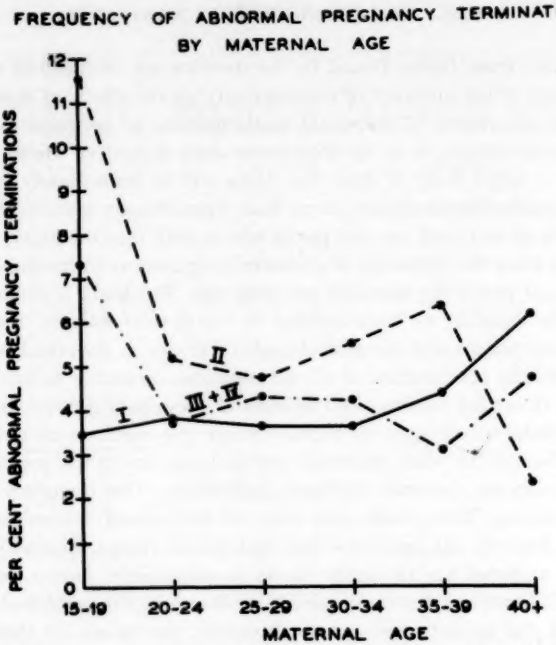

FIG. 1. The distribution of the frequency of abnormal pregnancy terminations by maternal age for the pregnancies of unrelated parents (I), first cousins (II), and first cousins once removed plus second cousins (III and IV).

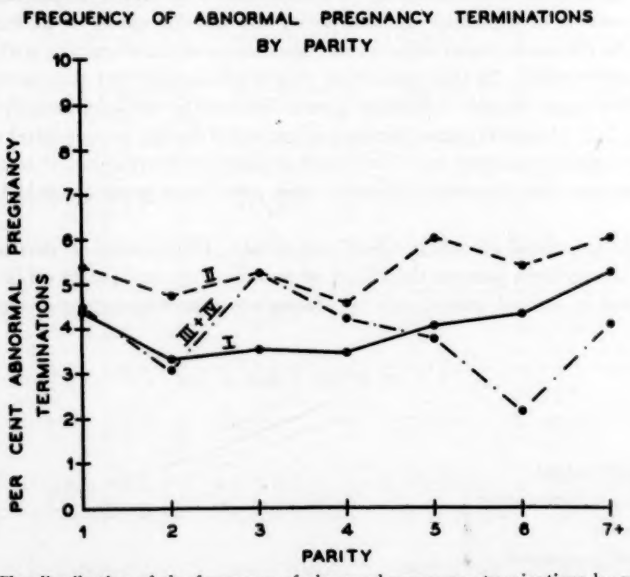

FIG. 2. The distribution of the frequency of abnormal pregnancy terminations by parity (birth rank) for the pregnancies of unrelated parents (I), first cousins (II), and first cousins once removed plus second cousins (III and IV).

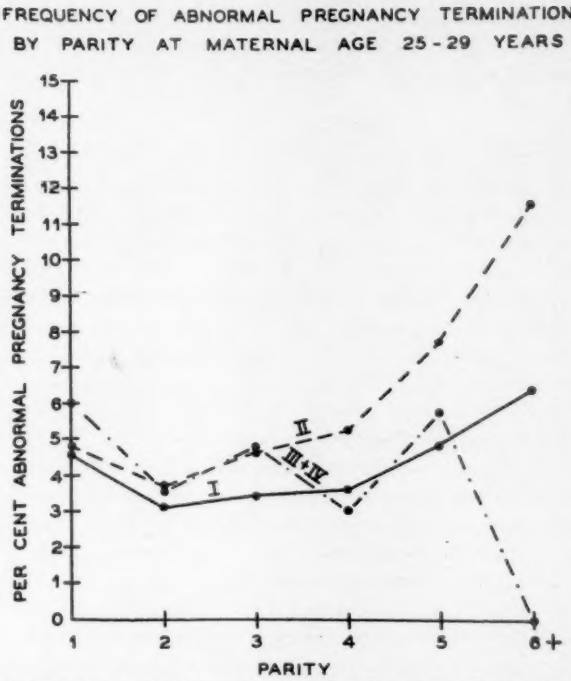

FIG. 3. The distribution of the frequency of abnormal pregnancy terminations by parity fo mothers 25–29 years old among the different classes of parental relationship (unrelated—I; firs cousins—II; first cousins once removed plus second cousins—III and IV).

and b_1, b_2, and b_3 are respectively the regression coefficients associated with parity, parity squared, and maternal age. Millis and Seng (1954) have shown that this same relationship is applicable to infants born in Singapore in the period 1950–1951.

It can be shown that if regressions of the type just described are fitted to the 12 city-consanguinity classes considering sexes separately and taking into account differences between the city-consanguinity classes in average birthweight, age, etc., the estimates of the regression coefficients from the various city-consanguinity classes are not significantly heterogeneous. The common regression equation for males is

$$\hat{y}_{ijk} = \bar{y}_{ij} + 9.188(x_{ijk} - \bar{x}_{ij}) - 0.672(w_{ijk} - \bar{w}_{ij}) - 0.192(z_{ijk} - \bar{z}_{ij})$$

and for females is

$$\hat{y}_{ijk} = \bar{y}_{ij} + 8.309(x_{ijk} - \bar{x}_{ij}) - 0.611(w_{ijk} - \bar{w}_{ij}) - 0.238(z_{ijk} - \bar{z}_{ij}).$$

The $\bar{y}_{ij}$, $\bar{x}_{ij}$, $\bar{w}_{ij}$, and $\bar{z}_{ij}$ are, respectively, the means in the ij^{th} city-consanguinity cell for birthweight, parity, parity squared, and maternal age. The regression coefficients are decagram increases (or decreases) in birthweight for unit changes in parity, maternal age, etc. Since the regression coefficients are not significantly hetero-

geneous, consanguinity does not appear to alter the relationship of maternal age and parity to birthweight. This is perhaps not surprising since the component of variation in birthweight ascribable to genetic factors in the fetus is small (Robson 1955, Morton, 1955).

THE EFFECT OF INBREEDING ON THE SEX RATIO

If there exist partially sex-linked lethal genes in man, one might expect an alteration in the sex ratio among the offspring of related parents. It has been shown that if related marriages occur at random, with respect to the four sex combinations through whom the relationship of husband and wife is traced, there will exist an excess of homozygous females (for details see Macklin, 1952). The amount of the excess, under random mating, is a function of the frequency of recombination of the locus in question with sex. In the absence of random mating, the ratio of affected females to affected males will be a function not only of the frequency of recombination but also of the true proportions of the four sex combinations through whom parental relationship occurs. Morton (1955) has shown that the different mating types of first cousins, first cousins once removed, and second cousins are non-randomly distributed in the Japanese. The departure from randomness, at least with respect to first-cousin matings, is not, however, sufficient to alter markedly the ratio of affected females to affected males from that obtaining under an assumption of random occurrence of the mating types.

Inspection of Table 17, where the distribution of male infants by city and parental relationship is given, fails to reveal any clear trends which might be construed as evidence for the existence of partially sex-linked lethal genes. Analysis of these data (see Table 18) reveals no significant effect of inbreeding on the frequency of male births.

In Table 18 and in the succeeding tables dealing with the analysis of the attributes of children born to related parents, we have presented or will present two analyses. Firstly, there is a chi-square analysis by the method of Roy and Kastenbaum (1956;

TABLE 17. THE DISTRIBUTION OF MALE INFANTS BY CONSANGUINITY AND CITY

City		Parental relationship				Total
		First Cousins	1½ Cousins	Second Cousins	Unrelated	
Hiroshima	n	936	313	384	26,012	27,645
	♂	478	153	196	13,550	14,377
	p	.5107	.4888	.5104	.5209	.5201
Kure	n	318	113	140	7,544	8,115
	♂	151	60	78	3,872	4,161
	p	.4748	.5310	.5571	.5133	.5128
Nagasaki	n	1,592	412	637	30,240	32,881
	♂	837	233	325	15,689	17,084
	p	.5258	.5655	.5102	.5188	.5196
Total	n	2,846	838	1,161	63,796	68,641
	♂	1,466	446	599	33,111	35,622
	p	.5151	.5322	.5159	.5190	.5190

TABLE 18. ANALYSIS OF THE RELATIONSHIP BETWEEN THE FREQUENCY OF MALE INFANTS AND CONSANGUINITY

a. Chi-square analysis

Source	χ^2	DF	P
Cities	1.435	2	.30–.50
Consanguinity	.803	3	.80–.90
Interaction	8.086	6	.10–.25
Total	10.324	11	.50–.70

b. Regression analysis

Source	χ^2	DF	P
Regression	0.052	1	.75–.90
Residual	0.765	2	.50–.75
Sum	0.817	3	

see also Roy and Mitra, 1956). If in this analysis significant differences between cities or a significant interaction of city with consanguinity obtains, then the regression analysis, the second method to be used, will be designed to allow for different city intercepts (means). If there is no demonstrable difference between cities nor an interaction between city and consanguinity, then the regression analysis will be based on the pooled consanguinity data. In the Roy and Kastenbaum method (see Roy and Mitra, 1956), the chi-squares associated with the "main effects" and "interaction" are independently distributed, but additivity is only in probability and asymptotically as $n \rightarrow \infty$. We have, therefore, computed the "interaction" in two ways, namely, (1) by formally solving the appropriate equations, and (2) by subtracting from the total chi-square the sum of the "main effects." In the tables, we have presented only the larger of these two chi-squares. This would seem to be a conservative procedure in that while one probably errs in asserting heterogeneity more frequently than it exists, the sole consequence of this is a more laborious regression analysis.

The regression analysis involves the fitting of a weighted regression of the natural logarithm of the proportion of survivors, or males, or non-malformed infants, as the case may be, on F, the coefficient of inbreeding. The genetic argument underlying this regression model is set forth in a paper by Morton, Crow, and Muller, 1956, and the basis on which the weights were computed will be found in Fisher's *Design of Experiments* (Section 68). It should, perhaps, be pointed out that in testing the fit of the regression model we have assumed that the various sums of weighted sums of squares of deviations from the mean, from the regression formula, and the reduction in the sums of squares of deviations in the dependent variable attributable to the regression are distributed as chi-square. While it can be shown that this is true for a normally distributed variable, when the weights are the informations with respect to the parameters being estimated, here, for a variety of reasons, an element of approximation exists. For convenience, the means and regression coefficients obtained by fitting this model to the data on sex ratio, malformations, and mortality are presented only once, and then in summary, in Table 35. In the Japanese data, as in

the French data analyzed by Morton, Crow, and Muller, the simple approximation $S = 1 - A - BF$ yields substantially the same slope B, and intercept, A, as obtained by fitting to S, the proportion of survivors, an exponential curve. We shall routinely test the common regression against a one-tailed alternative. In the case of the individual regressions, we shall also test against a one-tailed alternative provided the regression coefficients are all of the same sign. Since a test of the heterogeneity of the individual regression coefficients is sensitive to the magnitude of the coefficients as well as their signs, it may occur that a one-tailed test will be employed where the regression coefficients are clearly heterogeneous in magnitude but not in sign. This would not seem inappropriate since the regressions may agree in indicating an effect of consanguinity, but differ in the estimation of its importance. Clearly, two different questions are at stake.

THE EFFECT OF INBREEDING ON THE INCIDENCE OF MAJOR CONGENITAL MALFORMATIONS

Major congenital malformations are defined as those departures from normality which are incompatible with life or seriously limit the functioning of the individual, either directly or indirectly. Obviously, in the application of this definition to a series of malformations an element of subjectivity enters—there is no absolute division between "major" and "minor" malformations. We consider the malformations listed in Table 19 to be major congenital anomalies. Other patently major abnormalities which may occur to the reader either did not occur in this series of births, or, if they occurred, were unrecognized.

The distribution of infants with major congenital abnormalities by city and consanguinity will be found in Table 20. The frequency of infants with major congenital malformations increases significantly with increasing inbreeding (see Table 21). It would not appear that this association of consanguinity with the frequency of infants with major congenital defects is explicable in terms of residual maternal age and parity variation. The same general trend observable in Table 20 is clearly visible in Table 15 within those parity and age-specific cells where the entries are sufficiently numerous in all consanguinity classes to permit a judgment (e.g., parity 1 and maternal age 20–24 or parity 2 and maternal age 25–29).

The significant association of consanguinity with malformation rate suggests that some of the abnormalities listed in Table 19 arise as a consequence of homozygosity for a recessive gene or genes. We now ask, "Is it possible to form some judgment as to which malformations may be due to recessive genes?" In Table 22, the twelve most frequently occurring diagnoses are tabulated by parental relationship (a detailed presentation of the malformations found among the inbred and outbred children is presented elsewhere; see Neel, 1958, and Schull, 1958). Among the uncomplicated diagnoses, no one abnormality *clearly* suggests recessive factors. Complex anomalies appear, however, to be more frequent among the children of related parents. Conceivably some of the complex abnormalities are in fact hitherto unrecognized syndromes; if this is true, presumably some of these syndromes would have relatively simple modes of inheritance. Thus, it may be that the increase in the frequency of complex abnormalities reflects the increased probability of homozygosity for one

TABLE 19. AN ALPHABETICAL LISTING OF THOSE MALFORMATIONS OBSERVED IN THIS STUDY WHICH, OCCURRING ALONE OR IN COMBINATION WITH ONE ANOTHER, WERE GRADED AS MAJOR CONGENITAL DEFECT (AFTER NEEL AND SCHULL, 1956)

Achondroplasia
Albinism
Amputation, congenital
Anencephaly
Anonychia
Anophthalmos
Arthrogryposis
Atresia ani or rectum
Atresia of the external nares

Blepharophimosis
Brachydactyly

Cataracts
Central nervous system defect, severe
Claw hand
Cleft palate
Club foot
Coloboma iridis
Corneal defect
Cryptophthalmia
Cystic hygroma

Diaphragm, defect of
Diastasis recti, severe
Dislocations, multiple, congenital
Dysplasia of acetabulum, congenital

Ectodermal defect, congenital
Ehlers-Danlos syndrome
Encephalocele
Exostosis, severe, of bone
External ear, major malformation of

Facial cleft, oblique
Flexion deformity of fingers and toes
Foetus amorphous
Foetus papyraceous
Funnel chest

Gastroschisis

Harelip
Heart disease, congenital, cyanotic
Hemimelus
Hydrocephalus
Hypertelorism
Hypospadias, marked

Ichthyosis, congenita
Inguinal hernia (females)
Intestinal obstruction, congenital

Lymphangioma

Macroglossia
Major bone, absence of
Malformation, complex and ill-defined
Microcephaly
Micropenis
Microphthalmus
Microtia
Mongolism

Neurofibromatosis
Nystagmus, congenital

Oligodactyly
Omphalocele

Polydactyly
Polyostotic fibrous dysplasia
Polyoty
Ptosis of eyelids
Pupillary membrane, persistent

Radio-ulnar synostosis
Recto-vaginal fistula
Rhinencephaly

Situs inversus viscerum
Spina bifida with or without meningocele or meningomyelocele
Status Bonnevie-Ullrich
Sympodia
Syndactyly
Synorchism

Teratoma
Thyroglossal duct, persistent
Tumor, type undetermined

TABLE 20. THE DISTRIBUTION OF INFANTS WITH MAJOR CONGENITAL ABNORMALITIES BY CONSANGUINITY AND CITY

City		Parental relationship				Total
		First Cousins	1½ Cousins	Second Cousins	Unrelated	
Hiroshima	n	936	313	384	26,012	27,645
	m	17	2	4	293	316
	p	.0182	.0064	.0104	.0113	.0114
Kure	n	318	113	140	7,544	8,115
	m	4	2	1	58	65
	p	.0126	.0177	.0071	.0077	.0080
Nagasaki	n	1,592	412	637	30,240	32,881
	m	27	4	8	300	339
	p	.0170	.0097	.0126	.0099	.0103
Total	n	2,846	838	1,161	63,796	68,641
	m	48	8	13	651	720
	p	.0169	.0095	.0112	.0102	.0105

TABLE 21. ANALYSIS OF THE RELATIONSHIP BETWEEN THE FREQUENCY OF CONGENITAL MALFORMATIONS AND CONSANGUINITY

a. Chi-square analysis

Source	χ^2	DF	P
Cities	7.269	2	.02–.05
Consanguinity	11.775	3	.001–.01
Interaction	2.535	6	.75–.90
Total	21.525	11	.02–.05

b. Regression analysis*

Source	χ^2	DF	P
Individual regressions	7.262	3	.02–.05
Common regression	2.957	1	.02–.05
Heterogeneity	4.305	2	.10–.25
Residual	2.663	6	.75–.90
Sum within cities	9.925	9	

* In the absence of significant heterogeneity, one-tailed tests of significance will be used for the common and individual regressions.

or more recessively inherited, rare syndromes. Unfortunately, the data are not sufficiently numerous to permit a critical appraisal of this hypothesis.

It is interesting to note, at this point, that Yanase (1951) in his report on Shībamura also found multiple abnormalities in individuals born of a consanguineous marriage to be not infrequent. Haldane (1951) advanced evidence that unlinked genes may be associated as a consequence of the inbreeding which occurs in man. Whether the increase in multiple abnormalities reported here is a manifestation of the association of unlinked genes or represents pleiotropy cannot be determined with the data at hand.

There remains one other observation on the frequency of congenital malformation in these data worth considering, and this is the extent to which the observed associa-

TABLE 22. THE DISTRIBUTION OF TWELVE OF THE MORE COMMON AT-BIRTH DIAGNOSES BY CONSANGUINITY. FREQUENCIES ARE GIVEN AS THE NUMBER OF AFFECTED INFANTS PER 10,000 BIRTHS

Diagnosis	Parental relationship								Total
	First Cousins		1½ Cousins		Second Cousins		Unrelated		
Club foot	3	10.5	—	—	1	8.6	59	9.2	63
Polydactyly	1	3.5	1	11.9	—	—	38	6.0	40
Syndactyly	—	—	—	—	—	—	12	1.9	12
Polydactyly-syndactyly	—	—	—	—	—	—	11	1.7	11
Oligodactyly	2	7.0	—	—	—	—	5	0.8	7
Dysplasia of acetabulum	1	3.5	1	11.9	—	—	16	2.5	18
Atresia ani	1	3.5	—	—	1	8.6	5	0.8	7
Harelip with or without cleft palate	5	17.6	3	35.8	2	17.2	120	18.8	130
Simple cleft palate	6	21.1	—	—	—	—	29	4.5	35
Anencephalus	1	3.5	—	—	—	—	34	5.3	35
Anophthalmus and/or microphthalmus	2	7.0	—	—	—	—	13	2.0	15
Hydrocephalus	2	7.0	—	—	—	—	11	1.7	13
Complex anomaly including two or more of the above	3	10.5	—	—	—	—	25	3.9	28
Complex anomaly including one or more of the above*	6	21.1	1	11.9	3	25.8	46	7.2	56
Other	18	63.2	2	23.9	6	51.7	252	39.5	278

* With the exception of this group, all groups are mutually exclusive.

tion of inbreeding and malformation rate may be due to sex-linked recessive genes. The pertinent data arise as follows: Among the four classes of first-cousin marriages, an opportunity for homozygous females to occur due to the combination of derivatives of a gene present in one of the common ancestors exists only when the father and mother are the offspring of two sisters, or when the father is the son of a woman whose brother is the father of the mother. In these two instances, the coefficient of inbreeding with respect to sex-linked genes would be greater than zero; whereas, in the remaining two classes of first-cousin marriages, F would be zero. If the X-chromosome is contributing in any significant degree to the malformations here measured, then we may expect the malformation rate among the *female* offspring of spouses who are related as the children of sisters, or the son of a sister and the daughter of the sister's brother, to be greater than when the spouses are offspring of brothers or the daughter of a sister and the son of the sister's brother. In Hiroshima and Nagasaki combined, we have information on 190 pregnancies where the method of relationship of the parents is known, and where the pregnancy terminated in a female infant. The distribution of malformed infants is as follows:

	Type of First Cousins				
	Sis-Sis	Bro-Bro	SisSo-BroDa	SisDa-BroSo	Total
Malformed	7	3	4	3	17
Normal	50	34	51	38	173
Total	57	37	55	41	190

Two comments on these data are in order. Firstly, the malformation rate observed is not indicative of the malformation rate in the general population of related mar-

TABLE 23. THE DISTRIBUTION OF EARLY DEATHS BY CITY AND CONSANGUINITY. FOR A DEFINITION OF EARLY DEATHS REFER TO THE TEXT

City		Parental relationship				Total
		First Cousins	1½ Cousins	Second Cousins	Unrelated	
Hiroshima	N	919	311	380	25,719	27,329
	d	46	16	19	810	891
	p	.0501	.0514	.0500	.0315	.0326
Kure	N	314	111	139	7,486	8,050
	d	13	1	7	265	286
	p	.0414	.0090	.0504	.0354	.0355
Nagasaki	N	1,565	408	629	29,940	32,542
	d	66	8	18	1,016	1,108
	p	.0422	.0196	.0286	.0339	.0340
Total	N	2,798	830	1,148	63,145	67,921
	d	125	25	44	2,091	2,285
	p	.0447	.0301	.0383	.0331	.0336

riages because a long form, with the subsequent opportunity to determine the method of relationship, exists only on every tenth pregnancy termination, and every abnormal pregnancy termination. This series is, then, loaded with malformations, but the loading should be random if sex-linked genes are not involved in the etiology of the malformations observed. Secondly, from inspection of the data, it seems possible that the X-chromosome may be exerting a small effect since the malformation rate is 9.82 per cent when $F \neq 0$ and 7.69 per cent when $F = 0$. This difference, though in the direction specified by the hypothesis, is not significant.

THE EFFECT OF INBREEDING ON THE FREQUENCY OF EARLY DEATHS

For our purposes, we shall define early death as death during parturition or in the first month of life thereafter. Early deaths include, then, infants who were stillborn or who died in the first month of life, and *did not exhibit visible, gross abnormalities.*

The distribution of early deaths by city of birth and parental relationship is given in Table 23. From inspection of this table, it will be noted that, in general, the frequency of early deaths increases with increasing inbreeding. It will also be noted, however, that this apparent association of inbreeding and early death is not equally striking in the three cities. These impressions are borne out by analysis of the data (see Table 24). We see that the individual regressions remove a significant amount of variation, as does the common regression, but that the individual regressions are significantly heterogeneous. In short, though the cities are consistent in revealing an effect of inbreeding, they are inconsistent in revealing the magnitude of the effect. The reasons for this heterogeneity are not clear. One can, of course, ascribe it to sampling variation, but it is conceivable that the heterogeneity stems from residual variation in concomitant variables influencing pregnancy outcome. We shall return to these data shortly, and consider whether the same heterogeneity exists if one partitions early deaths into (a) stillbirths, and (b) livebirths terminating in death in the first thirty days of life.

TABLE 24. ANALYSIS OF THE RELATIONSHIP BETWEEN THE FREQUENCY OF EARLY DEATH AND CONSANGUINITY

a. Chi-square analysis

Source	χ^2	DF	P
Cities	1.954	2	.25–.50
Consanguinity	12.108	3	.001–.01
Interaction	14.462	6	.01–.025
Total	28.524	11	<.001

b. Regression analysis

Source	χ^2	DF	P
Individual regressions*	10.959	3	<.01
Common regression*	2.924	1	<.05
Heterogeneity	8.035	2	.01–.025
Residual	10.289	6	.10–.25
Sum within cities	21.247	9	

* One-tailed test.

TABLE 25. THE DISTRIBUTION OF DEATHS IN THE FIRST NINE MONTHS OF LIFE BY CITY AND CONSANGUINITY

City		Parental relationship: First Cousins	1½ Cousins	Second Cousins	Unrelated	Total
Hiroshima	n	335	107	139	8,606	9,187
	d	24	4	8	392	428
	p	.0716	.0374	.0576	.0455	.0466
Nagasaki	n	487	125	177	8,725	9,514
	d	30	1	10	416	457
	p	.0616	.0080	.0565	.0477	.0480
Total	n	822	232	316	17,331	18,701
	d	54	5	18	808	885
	p	.0657	.0216	.0570	.0466	.0473

THE EFFECT OF INBREEDING ON INFANTILE AND CHILDHOOD MORTALITY

As has been previously indicated, a sample of the infants seen at birth was selected for examination in the central clinical facility at the age of nine months. This second observational period permits extending the data on mortality to include the first nine months of life as well as the perinatal period.

Inspection of Table 25, where the distribution of deaths in the first nine months of life is given by city and consanguinity, suggests the possibility of an association; however, it will be noted that in both cities there is an apparent depression of the death rate among the children born to parents related as first cousins once removed. In Table 26 are given the results of analyzing these data. The consanguinity classes differ significantly one from another, and there is no city difference nor evidence of city-consanguinity heterogeneity. It would be appropriate, therefore, to measure the effect of inbreeding on the pooled city data. When this is done, one notes that

TABLE 26. ANALYSIS OF THE RELATIONSHIP BETWEEN THE FREQUENCY OF DEATH IN THE FIRST NINE MONTHS OF LIFE AND CONSANGUINITY

a. Chi-square analysis

Source	χ^2	DF	P
Cities	0.217	1	.50–.75
Consanguinity	10.411	3	.01–.02
Interaction	1.769	3	.50–.75
Total	12.397	7	

b. Regression analysis

Source	χ^2	DF	P
Regression*	3.290	1	.025–.05
Residual	5.175	2	.05–.10
Sum	8.465	3	

* One-tailed test.

TABLE 27. THE DISTRIBUTION OF THE SAMPLE SELECTED FOR STUDY IN HIROSHIMA IN 1956 BY CONSANGUINITY

Consanguinity	Recontacted	Moved from city	Unable to locate	Total
First cousins	352	35	32	419
1½ cousins	106	17	13	136
Second cousins	144	13	18	175
Unrelated	567	74	78	719
Total	1169	139	141	1449

the regression does remove a significant amount of variation. There exists, then, a significant association of inbreeding with mortality in the first nine months of life.

Still a third body of data exists on the relationship of consanguinity to mortality. In the summer of 1956, an attempt was made in a selected sample to determine the frequency of death in the first eight years of life. For this purpose, 1500 pregnancy registrations were selected in Hiroshima. These registrations were selected from the years 1948–1949, and represented (a) the first 750 liveborn children to be recorded in the genetics program whose parents were related, and (b) the first 750 liveborn "zero" infants (infants whose registration numbers terminated in zero) whose parents were unrelated. After selection, multiple births were excluded leaving 1490 infants in Hiroshima to be studied. An effort was then made to revisit the parents of these infants to determine whether the child was still alive, and if not alive, the cause and date of death. In Table 27 are presented the numbers of successful and unsuccessful attempts to revisit for the various classes of parental relationship. Inspection of this table reveals several items of interest. Firstly, it should be noted that the related parents show a lower migration rate than that exhibited by the unrelated parents. This may be a manifestation of the same sense of family unity which motivated these individuals to select relatives for their spouses. Secondly, among the unsuccessful attempts to revisit within each class of relationship, approximately half are cases where the parents are known to have moved from the city and the other half could not be located.

TABLE 28. THE DISTRIBUTION OF MATERNAL AGE AMONG RELATED AND UNRELATED PARENTS WHO WERE OR WERE NOT CONTACTED IN 1956

Hiroshima

Group	n	$\bar{x}$	s^2
Contacted:			
Related parents	601	27.09	28.15
Unrelated parents	565	27.72	28.12
Not contacted:			
Related parents	128	25.95	26.34
Unrelated parents	152	26.23	22.35

Homogeneity of the means

Source	S.S.	DF	M.S.	F
Relationship	95.59	1	95.59	3.49
Contact	378.77	1	378.77	13.84**
Interaction	25.59	1	25.59	1.07
Between classes	499.96	3	166.65	6.09**
Within classes	39,470.37	1,442	27.37	
Total	39,970.33	1,445		

Homogeneity of the variances

$\chi^2 = 3.398$ DF = 3

In view of the differential rates of attrition among the related and unrelated parents, to draw valid inferences from the data collected requires demonstrating that the migrating individuals do not differ appreciably from the non-migrating persons, or if differences do exist that such differences are the same among the related and unrelated parents. Some data relevant to this point exist. In Table 28 are given the results of comparing, for the related and unrelated groups, the ages of mothers who have remained in the city with the ages of those who have moved from the city or cannot now be located (the disparity between this table and Table 27 is due to the exclusion of 3 mothers whose ages were not recorded at the follow-up). It is to be noted that while mothers who have moved from the city are, on the average, significantly different in age (younger) than those who have not moved, there is no indication from the interaction that this age difference is dissimilarly distributed in the related and unrelated groups. Equivalent findings can be demonstrated with regard to the mean number of pregnancies experienced by related and unrelated mothers living in and outside the city. The age and parity differences obtaining among the related and unrelated parents would appear to be such as to lead to an inflation of the death rate particularly in the first year of life among the offspring of unrelated parents. Residual concomitant variation may, then, minimize the significance of the data on mortality in the first eight years of life.

In Table 29 are distributed the deaths in the first eight years of life by parental relationship. At a glance, it would appear that childhood mortality is associated with inbreeding in Hiroshima. Upon analysis of these data (see Table 30), we find a significant association of the variable with consanguinity. In an attempt to reenforce this finding, Table 31 is presented (a small discrepancy between Tables 29 and 31 exists because of the failure to record age at death for one of the children born to first cousins once removed). In this table, it will be noted that the deaths occurring

TABLE 29. THE DISTRIBUTION OF DEATHS IN THE FIRST EIGHT YEARS OF LIFE IN HIROSHIMA BY CONSANGUINITY

	Parental Relationship				
	First Cousins	1½ Cousins	Second Cousins	Unrelated	Total
Total infants	352	106	144	567	1,169
Deaths	41	9	8	31	89
Proportion	.1165	.0849	.0556	.0547	.0761

TABLE 30. ANALYSIS OF THE RELATIONSHIP BETWEEN THE FREQUENCY OF DEATH IN THE FIRST EIGHT YEARS OF LIFE AND CONSANGUINITY

Source	χ^2	DF	P
Regression	10.119	1	<.001
Residual	0.432	2	.75–.90
Sum	10.552	3	.01–.025

TABLE 31. A PARTITION OF DEATHS IN THE FIRST EIGHT YEARS OF LIFE IN HIROSHIMA

	Death in first year			Death between 1–8 years of life		
Consanguinity	n	d	p	n	d	p
First cousins	352	26	0.0739	326	15	0.0460
1½ cousins	106	5	0.0472	101	3	0.0297
Second cousins	144	5	0.0347	139	3	0.0216
Unrelated	567	23	0.0406	544	8	0.0147
Total	1,169	59	0.0505	1,110	29	0.0261

in the first eight years of life have been partitioned into two groups, namely, deaths in the first year, and deaths between years 1 and 8 of life. Now we may surmise that deaths in the first year of life should agree reasonably well with the values obtained in the first nine months of life (see Table 25) if the inbreeding effect here observed is real. From a comparison of Tables 25 and 31, we see that the two different estimates are sensibly the same. It is equally clear that the results obtained at eight years of age are not wholly explicable in terms of the effect of inbreeding on death in the first year of life. Inbreeding effects are not confined, then, to a single stage in life.

Before we attempt to summarize the data on the association of inbreeding with infantile and childhood mortality, let us return to the data on early deaths and examine the results of partitioning these data into (a) stillbirths, and (b) neonatal deaths, i.e., deaths in the first month of life. In Table 32 is given the distribution of stillborn infants by city and parental relationship. The distribution of neonatal deaths, which will not be presented, can be obtained by the reader by subtracting the number of stillborn infants in each city-consanguinity cell from the number of infants at risk and from the number of early deaths in that cell as given in Table 23. Inspection of Table 32 suggests that in Kure and Nagasaki the effect of inbreeding on the frequency of stillborn infants is small and contrary to the genetic hypothesis. Hiroshima, however, supports the notion of an appreciable inbreeding effect. Analysis of these data (see Table 33a) fails to reveal heterogeneity among the regression coefficients, or that a significant amount of variation is removed by either the common

TABLE 32. THE DISTRIBUTION OF STILLBORN INFANTS BY CITY OF BIRTH AND PARENTAL RELATIONSHIP

City		Parental relationship: First Cousins	1½ Cousins	Second Cousins	Unrelated	Total
Hiroshima	n	919	311	380	25,719	27,329
	s	19	6	6	345	376
	p	.0207	.0192	.0158	.0134	.0138
Kure	n	314	111	139	7,486	8,050
	s	5	1	4	144	154
	p	.0159	.0090	.0288	.0192	.0191
Nagasaki	n	1,565	408	629	29,940	32,542
	s	22	3	9	443	477
	p	.0141	.0074	.0143	.0148	.0147
Total	n	2,798	830	1,148	63,145	67,921
	s	46	10	19	932	1,007
	p	.0164	.0120	.0166	.0148	.0148

TABLE 33. a. ANALYSIS OF THE RELATIONSHIP OF INBREEDING TO THE FREQUENCY OF STILLBIRTHS

Source	χ^2	DF	P
Individual Regressions*	3.457	3	.12–.25
Common Regression*	0.061	1	.37–.45
Heterogeneity	3.396	2	.10–.25
Residual	2.767	6	.75–.90
Sum (within cities)	6.224	9	

b. ANALYSIS OF THE RELATIONSHIP OF INBREEDING TO THE FREQUENCY OF NEONATAL DEATH

Source	χ^2	DF	P
Individual Regressions*	10.425	3	.001–.01
Common Regression*	3.649	1	.025–.05
Heterogeneity	6.776	2	.025–.05
Residual	9.522	6	.10–.25
Sum (within cities)	19.947	9	

* One-tailed test.

regression or the pooled individual regressions. The common regression coefficient is positive, and therefore in the direction of the hypothesis of an inbreeding effect. Analysis of the neonatal death data (see Table 33b) proves to be very much like the findings for early deaths in that (1) all of the regression coefficients are positive, (2) the common regression and the individual regressions remove a significant amount of variation, and (3) the individual regressions, though all positive, are significantly different in magnitude. It would appear, however, that removal of the stillbirths has somewhat reduced the heterogeneity from that in the case of the early deaths. This latter statement is based on the heterogeneity tests in the two instances.

One final observation regarding the data on stillbirths and neonatal deaths seems pertinent. If one compares the stillbirth rate among the pregnancies of unrelated

parents with that obtaining among the pregnancies of related parents (all classes of consanguineous marriages pooled) for each city and year (ignoring the year 1954 in Hiroshima and Nagasaki), one finds that among the fifteen possible comparisons the stillbirth rate among the offspring of related parents exceeds that among the offspring of unrelated parents in only eight instances. This number of exceedances is clearly not significant on a sign test. A similar analysis of the neonatal death rates, on the other hand, reveals that in twelve of fifteen comparisons the death rate is higher among the offspring of related parents. This is clearly significant on a sign test. The data are, then, internally consistent in revealing an effect of inbreeding on neonatal mortality while failing to reveal an effect of inbreeding on the frequency of stillbirths.

We are faced with the problem of accounting for the heterogeneity between cities in the effects of inbreeding on the frequency of stillbirths and neonatal deaths. With respect to the latter variable, the heterogeneity is, perhaps, not too difficult to rationalize. One may argue for the existence of differences in the regression coefficients as follows: In a certain sense, most, if not all, "genetic deaths" involve the interaction of a specific genotype with environmental factors. Clearly we may visualize a spectrum of interactions ranging from, say, what might be termed absolute deaths (the genotype is incompatible, with any known environment) to situations where the genotype is compatible, in at least some degree, with all environments. Amelioration of the environmental factors which in association with a specific genotype leads to death should produce a relatively greater reduction in deaths among the offspring of parents who are related, than among the offspring of parents who are unrelated, since the requisite genotype is proportionately more frequent. This would, of course, lead to a decline in the value of the regression coefficient. During periods of rapid and substantial improvement in the environment, a temporal trend in the value of the regression coefficient might be demonstrable. In view of the known differences between Hiroshima, Kure, and Nagasaki, it is not at all inconceivable that amelioration may have occurred in different ways and to different extents in the three cities. One may argue, as a matter of fact, that identical estimates would be most unexpected since this would require that the mean fitness of these three populations, with reference to the loci measured, be the same. On an *a priori* basis, this would be hard to believe in view of the differences in the concomitant variables affecting mortality, and the possible genetic differences in these three groups of people.

The heterogeneity with respect to the stillbirth data admits of several intriguing explanations. Perhaps, the most conservative one proceeds as follows: Clearly the survival of a liveborn child depends upon the genotype of that child and the environmental stresses to which it is subject. The survival, however, of a fetus is a much more complex phenomenon involving the interaction of fetal genotype, maternal genotype, and maternally mediated environmental factors. In this nexus of interactions, it is possible that the stillbirth component attributable to fetal genotype is overshadowed by the maternal genotype and environmental stresses mediated through the mother. This overshadowing of the fetal genotype could result in a failure to detect an inbreeding effect on stillbirths when an inbreeding effect on neonatal mortality was clearly demonstrable. Moreover, an amelioration of the maternally mediated environmental stresses in one area but not in others could result

in a detection of an inbreeding effect in one city not demonstrable in the others. Furthermore, it is conceivable that this amelioration of environmental stresses mediated through the mother could occur independently of any amelioration of the environmental stresses on the liveborn child, and, as a consequence, one might find a relatively high association of inbreeding and stillbirth in conjunction with an equally high, or higher association of inbreeding and neonatal mortality.

To summarize the mortality data, we find the following:

(1) The role of inbreeding in the etiology of stillbirths cannot clearly be determined from these data. Hiroshima suggests an effect of inbreeding on the stillbirth rate; whereas Kure and Nagasaki fail to reveal an association between these two variables. In Kure and Nagasaki not only are the regression coefficients not significantly different from zero, but the estimates are actually negative in sign.

(2) A significant, positive association of inbreeding with death in the first month of life appears in all three cities. The magnitude of this effect varies from one city to another presumably due to environmental differences and/or residual concomitant variation.

(3) In the first 9 months of life, Hiroshima and Nagasaki are consistent in proclaiming an effect of inbreeding on mortality during this period of life.

(4) Finally, evidence from Hiroshima suggests that inbreeding continues to exert a measurable influence on mortality beyond the first year of life and to the eighth year of life, the upper age limit of this study.

THE INFLUENCE OF INBREEDING ON PREGNANCY WASTAGE AS MEASURED BY ANAMNESTIC DATA

One further approach to the problem of the relationship of consanguinity to pregnancy termination remains to be discussed. It has been argued that since (1) offspring of consanguineous marriages run an increased risk of homozygosity for deleterious recessive mutants, and since (2) homozygosity for such mutations may be manifested as abortions occurring before the mother is aware of her pregnancy, the mean interval between the beginning of cohabitation for a couple and the termination of the first recognizable pregnancy may bear a relationship to the biological relatedness of the cohabiting couple. To explore this possibility all first-born children were tabulated by parental relationship and the interval, in months, between the registration of the pregnancy and the beginning of cohabitation on the part of the parents. These data are presented in Table 34. Obviously to draw inferences from these data requires certain assumptions. Among the most important of these are (1) whatever element of family planning there is in Japan, it is the same in all classes of parental relationship; (2) the beginning of cohabitation is accurately and reliably reported in all classes of relationship; and (3) the interval between eligibility to register and actual registration is the same in all consanguinity classes. It is patently impossible to assert that these assumptions are fulfilled by the data or that they are not fulfilled. We have seen, for example, that there is evidence that the various consanguinity classes differ with regard to the frequency of mothers reporting therapeutic interruptions. Since a therapeutic interruption of a pregnancy is a socially acceptable means of regulating family size in Japan, we may interpret the observed differences among the consan-

TABLE 34. MONTHS OF COHABITATION PRIOR TO THE REGISTRATION OF FIRST PREGNANCY

Months	Parental Relationship			
	First Cousins	1½ Cousins	Second Cousins	Unrelated
1	1	1	—	24
2	1	—	—	18
3	—	—	—	56
4	26	8	8	721
5	54	14	25	1,998
6	72	20	30	2,114
7	52	18	26	1,816
8	51	15	23	1,612
9	41	8	16	1,281
10	38	16	18	1,055
11	35	7	13	862
12	31	7	11	742
13	22	2	11	610
14	13	8	9	480
15	18	5	6	413
16	14	6	13	365
17	12	6	8	309
18	6	3	5	259
19	6	2	3	240
20	7	1	3	186
21–22	13	6	10	318
23–24	15	2	4	265
25–26	9	—	4	191
27–28	6	1	3	145
29–30	10	2	5	135
31–32	6	—	2	95
33–34	1	2	1	82
35–36	3	1	1	73
37–38	3	—	—	65
39–40	6	1	—	75
41–42	5	—	1	58
43–44	4	—	1	46
45–46	4	—	1	42
47–48	1	—	1	40
49–50	1	1	3	29
51–52	4	—	1	23
53–54	2	—	—	23
55–56	1	—	—	22
57–58	—	—	—	20
59+	8	2	2	291
Total	602	165	268	17,199

guinity classes as evidence of differences in family planning or, perhaps, in notions of the desirable size of family. The fact that differences do obtain need not necessarily vitiate the approach proposed since the observed differences would appear to lengthen the interval in the unrelated class. This would seem to follow for we know that frequently pregnancies which occur very shortly after marriage are interrupted so that the wife may continue to work until a greater measure of economic security is attained. Because of the higher frequency of induced abortions among the unrelated

parents presumably more first pregnancies are also interrupted. These cases would not enter the present tabulation which is restricted to first pregnancies where the gestation was of at least 21 weeks duration. The net effect would be to exclude a proportionately greater number of very short intervals among the unrelateds than among the relateds with the consequent increase in the mean interval for the unrelated parents. This would, of course, tend to minimize a consanguinity effect, if present.

One of the major factors determining the lag between eligibility to register a pregnancy and actual registration must be economic, reflecting the need for the supplementary rations, etc. which are available upon registration. Since marked differences in the distribution of economic statuses among parental relationships do not obtain, we may surmise that motivation is similar among the classes, and presumably the intervals between eligibility and actual registration would be similar. These speculations do not, of course, establish that the assumptions enumerated above are met by these data, but they do afford one some measure of confidence that the assumptions may be approximately fulfilled.

Inspection of Table 34 fails to reveal any striking differences among the classes of relationship. We note that in all four instances the modal interval is six months. The means and medians show some slight shift to the right when the parents are related; however, the magnitude of the shift bears no clear relationship to the coefficient of inbreedings as can be seen from the following figures:

	Median	Mean
Unrelated parents	9	12.19 months
First Cousins	10	13.56 months
1½ Cousins	9	11.92 months
Second Cousins	10	13.05 months

In view of the smallness of the differences among the consanguinity classes and the largeness of the sources of concomitant variation, it seems doubtful that one can attribute the observed shifts to a consanguinity effect with much measure of assurance.

OTHER STUDIES IN JAPAN ON THE EFFECTS OF CONSANGUINEOUS MARRIAGES

It is informative at this juncture to review briefly some of the Japanese studies on the effects of consanguinity since virtually all of these studies are inaccessible to workers outside Japan for reasons of language.

In general, the Japanese studies have taken one or the other of two forms. As has been indicated, a number of investigations have been made on the so-called "consanguinity villages" in Japan, and information of a variety of sorts has been collected. Within the "consanguinity villages" since virtually all individuals are related to some degree, and since degree of inbreeding has often not been considered, analysis of the data has involved the comparison of the results obtained in the "consanguinity village" with an adjacent village where consanguineous marriages are uncommon, or with the values characteristic of the prefecture in which the village is situated. A second type of study has involved villages or towns sufficiently large that a comparison of children whose parents were unrelated with children whose parents were related

is possible. Regression methods have not been employed in analyzing any of these studies, and the published accounts of the data preclude the use of such methods by others. The samples of related individuals available for study have generally been small regardless of the method of study.

Two Japanese studies appear especially germane to the data presented here, namely, the work of Ichiba (1953, 1954) on school age children in Gifu, Nagano and Fukushima Prefectures and the work of Shiroyama (1953) and Shiroyama and Shiroyama (1953) on pre-school age and school age children in Miyazaki Prefecture.

Ichiba has studied 2,829 children in grades 1 to 6 living in Itadori, Gifu; Ina, Nagano; Katagiri, Nagano; Okisawa, Fukushima; and Sekihara, Tokyo. Of this number, 190 children are of consanguineous parents. A rather extensive array of anthropometric, physiological and psychological measures was obtained. Among the measurements were chest width, chest breadth, chest length, length of sternum, length of trunk, head girth, pelvis width, neck girth, abdominal girth, waist girth, head width, span, chest angle, sitting height, grasping power, 50 meter run, Tanaka Type B Intelligence Test, and appraisals of temperament. The effect of consanguinity was assayed by converting the observed measures on the 2,829 children to standard measure and then observing whether the measurements on the consanguineous group were uniformly distributed around zero. For the fourteen anthropometric measurements in every instance more than fifty per cent of the children born to consanguineous marriages exhibit measurements which are less than the average for the 2,829 children who were investigated. For each of the two physiological measures, more than fifty per cent of the children of related parents were below the means of the whole group. Finally, on the intelligence test a greater percentage of the children of consanguineous parents were found to be dull than was true of the children of unrelated parents. Ichiba infers that there may be a general shift of the I.Q. distribution since the extremes of the I.Q. distributions are not appreciably different for the two classes of children. Ichiba summarizes his data by asserting that the effects of consanguinity on the variables which he studied must be small if existent at all.

Shiroyama (1953), in a study conducted in Kiyotake-mura, Miyazaki Prefecture, in 1948, obtained birthweights, heights, weights, and chest circumferences on 121 children (63♂) born to related parents in the years 1943–1948, and on 858 children (430♂) born to unrelated parents in the same time period. He failed to demonstrate significant differences in birthweight, chest girth, height, or weight. However, it is interesting to note that of the fourteen possible comparisons between the children of related and unrelated parents when sex and year of birth are taken into account in 11 instances the mean birthweight for the child of consanguineous parents is less than the mean birthweight of the child of unrelated parents.

In another study, Shiroyama and Shiroyama (1953) investigated the mental development of some 374 children of whom 48 were the offspring of related parents. A significantly greater proportion of the children of related parents exhibited I.Q.s of less than 70 than was true among the children of unrelated parents (related: 8 out of 48; unrelated: 19 out of 326; $\chi^2 = 7.338$, DF = 1).

Shinozaki (1955), Shinozaki and Aoki (1951), and Shinozaki, Yoshida, and Aoki

(1951) have reported results obtained from the investigation of three "consanguinity villages." These are Narata to which previous reference has been made, Nanaura and Hata buraku of Toyobusa-mura in Chiba Prefecture, and Akiyamagō which lies partly in Nagano and partly in Niigata Prefecture. Narata and Akiyamagō are mountain villages of 957 and about 1200 persons respectively; Nanaura and Toyobusa-mura are coastal, fishing-farming villages of about 5,241 individuals. The economies of Narata and Akiyamagō are marginal and the general nutritional status is poor. Nanaura and Toyobusa-mura, on the other hand, enjoy an appreciably better economy, and food is ample, if not abundant. The studies were conducted in 1943 (Narata), 1948 (Akiyamagō), and 1950 (Nanaura and Toyobusa-mura). In all three instances, the authors advance evidence suggesting a lowered birth rate; thus, the birth rate in Narata was 29 per 1000 at a time when the national average was 35 (1940), Akiyamagō had a birth rate of 26.4 when the national average was 33.8 (1948). The data for Nanaura and Toyobusa-mura are presented as Pearl's "rate of pregnancy," and the values obtained were 33.6 for related parents and 43.9 for unrelated parents. Stature was below normal in Narata and Akiyamagō, but equal to the national average in Nanaura and Toyobusa-mura. In all three studies, however, physical capacity as measured by grasping power, strength of back muscles, etc. was below normal. The onset of menstruation was 16–17 years in Narata, 15.6 years in Akiyamagō, and 15.3 years in Nanaura and Toyobusa-mura as contrasted with the national average of about 14.6 years. No unusual incidence of clearly inherited recessive, autosomal or sex-linked, pathologies was found in Narata or Nanaura. In Akiyamagō, on the other hand, 24 per cent of the males and 2 per cent of the females exhibited red-green colorblindness.

One other study which deserves mentioning is the work of Yanase (1951). Yanase studied the physical well-being of individuals residing in four villages in Western Japan with relatively high rates of consanguineous marriage. These villages were Shība-mura, Miyazaki Prefecture; Kariya-mura, Yamaguchi Prefecture; Shika-mura and Shikanoshima-mura, Fukuoka Prefecture. Shība-mura and Shika-mura are mountain villages whereas Shikanoshima-mura and Kariya-mura are coastal villages. Yanase finds that each of these villages has its own quantitative and qualitative peculiarities. Thus, Shība-mura exhibits a relatively high frequency (5.4 per cent) of heterochromia iridis not found in the other villages; cataracts and lateral epicanthus are common in Shikanoshima-mura. Moreover, within Shība-mura, specific abnormalities have restricted geographical distributions, and though the defects occur more frequently among the offspring of consanguineous marriages they are found among the offspring of individuals not known to be related. Among the offspring of individuals not known to be related, the frequency is higher when both parents come from the same *aza* than when both parents are drawn from the same *chiku*. Neither the *chiku* nor the *aza* are regular units of measure in the sense, say, that the terms township and section, where used in the United States, define fixed areas of land, namely, 36 and 1 square mile respectively. As a general rule, a *chiku* is larger than an *aza*.[4]

[4] Japanese terms such as *aza*, *chiku*, *buraku*, etc. are no less confusing than their English counterparts, and are equally defiant of rigid definition. The term *mura* is applied to an administrative

AN ESTIMATE OF THE MUTATIONAL DAMAGE IN MAN

Recently several different methods for estimating the mean number of deleterious mutants in man which homozygously would lead to the death of an individual between birth and maturity have been advanced (see Slatis, 1954; Morton, Crow, and Muller, 1956; Krooth, 1957). All of these methods employ, as the basis of estimation, the detrimental effects of consanguineous marriage.

Morton, Crow, and Muller (1956) estimate that, on the basis of data collected by Sutter and Tabah (1953, 1954), Arner (1908), and Bemiss (1858), "the average gamete carries a group of detrimental factors that, if dispersed in separate individuals and made homozygous, would result in 1.5–2.5 deaths of that age group. Thus the total genetic damage here measured is 1.5–2.5 lethal equivalents per gamete, or 3–5 per zygote." A lethal equivalent is defined as "a group of mutant genes of such number that . . . they would cause on the average one death, e.g., one lethal mutant, or two mutants with 50 per cent probability of causing death, etc."

Several tests for internal consistency of the various collections of consanguinity data were made by Morton, Crow, and Muller, 1956. We reproduce, for comparative purposes, their findings with regard to the data of Sutter and Tabah whose study was more nearly comparable to the Japanese than those of Arner or Bemiss. The regression coefficients B, B_{FF}, B_{FO}, and B_{CO} reproduced in Table 35 are, respectively, the regression coefficients obtained by using (1) all different degrees of consanguinity (unrelated, second cousins, 1½ cousins, and first cousins), (2) the different degrees of consanguinity omitting completely the noninbred group, (3) the noninbred group and the average of all inbred groups, and (4) the noninbred and the first cousin marriages only. In Table 35, we also present the corresponding values obtained in Hiroshima, Kure, and Nagasaki. Within these data, comparison of B_{FF} with B_{FO} affords a measure of internal consistency. Only the early death data from Hiroshima and Nagasaki are inconsistent by this criterion. No single explanation appears to account for this inconsistency.

To compare meaningfully the entries in Table 35, certain differences in definition and method of data collection between the French and Japanese studies must be borne in mind. Thus,

1. The French study was retrospectively oriented, and involved a sample of marriages contracted in a given time period, 1920–21 in the district of Morbihan, and 1919–25 in the district of Loir-et-Cher. The Japanese study was prospectively oriented, and included virtually all of the marriages producing a pregnancy lasting for at least five months during 1948–1954 in Hiroshima, Nagasaki and Kure. Sutter and Tabah have investigated a more or less sedentary population which was rural to rural-urban; the study in Japan encompasses a definitely urban area and a some-

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village. The *mura* may be subdivided, area-wise, into *Ōaza* or *aza* which need not be and generally are not, of equal size. Frequently the population encompassed by a *mura* will not be continuously distributed over the area which the *mura* includes. There exists an opportunity, then, for discrete collections of houses which in English might be termed hamlets, but, in Japanese, are *buraku*. The *chiku* merely refers to an area in the same vague sense in which we might speak of the northwest section of a city.

TABLE 35. A COMPARISON OF THE EFFECTS OF INBREEDING IN JAPAN WITH THOSE FOUND IN FRANCE

Source of data	A	B	B/A	B_{FF}	B_{FO}	B_{CO}
Morbihan						
Stillbirths-neonatal deaths	.0460	1.124	24.43	.901	1.233	1.163
Infant-juvenile deaths	.0950	1.431	15.06	.937	1.665	1.222
Total	.1410	2.555	18.12			
Loir-et-Cher						
Stillbirths-neonatal deaths	.0335	.574	17.12	.398	.662	.538
Infant-juvenile deaths	.0558	.908	16.26	1.201	.759	1.141
Total	.0893	1.482	16.60			
Hiroshima						
Malformations	.0113	.084	7.43	.193	.062	.112
Early deaths	.0322	.371	11.52	−.007	.432	.310
Death in 9 months	.0465	.395	8.49	.450	.383	.444
Death in 8 years	.0543	1.076	19.82	1.392	.982	1.082
Total*	.0763	1.231	16.13			
Kure						
Malformations	.0077	.099	12.86	.071	.104	.079
Early deaths	.0360	.044	1.22	.042	.042	.100
Total	.0437	.143	3.27			
Nagasaki						
Malformations	.0099	.108	10.91	.114	.107	.115
Early deaths	.0343	.091	2.65	.355	.034	.138
Death in 9 months	.0487	.144	2.96	.373	.096	.235
Total*	.0722	.234	3.24			

* The totals are derived from summing malformations, death in 8 years (or in 9 months in the case of Nagasaki), and that component of early deaths due to stillbirths.

what more mobile population. Information on the inbred and outbred groups was obtained in different fashions in the case of Sutter and Tabah's study; this was not true for the work in Japan.

2. In the Japanese study, each marriage is represented, on the average, by 1–2 children whereas in the French data each marriage is represented by about 3.5–4.5 children, on the average.

3. Stillbirths and neonatal deaths, in the French data, include late miscarriages, stillbirths, and deaths in the first month of life. Conspicuous abnormality may or may not have been present. Early deaths in the Japanese study include late miscarriages, stillbirths, and deaths in the first month of life without conspicuous abnormality.

4. Infantile and juvenile deaths in the French data include deaths from one month of age to, presumably, the maximum age which might be attained by the offspring of parents who had been married 25–30 years. Death in 9 months or death in 8 years in our data include deaths among liveborn, non-malformed infants at any time after birth until 9 months or 8 years as the case may be. There are, of course, numerous other differences between the studies most of which are functions of the different cultural milieu in which the studies were conducted. The effect of these differences on the data cannot be readily evaluated.

Any comparison of the values given in Table 35 is not without danger. In the strict

sense, the estimates of A and B have meaning only with reference to the particular set of environmental circumstances obtaining in the areas under consideration. And certainly there is no reason for believing that the environmental stresses in Loir-et-Cher or Morbihan are the same, or even similar, to those in Hiroshima, Kure, or Nagasaki. Clearly, then, a comparison of the absolute values of A and B has little meaning. A somewhat more meaningful comparison involves the ratio of B to A. The latter may be viewed as an index of the relative importance of inbreeding. In a comparison of the values in Table 35, the ratio B to A obtained from summing malformations and early deaths in Hiroshima and Nagasaki is to be compared with the values obtained for stillbirths-neonatal deaths in Morbihan or Loir-et-Cher. Similarly, the total for Hiroshima should be roughly comparable to the totals for Morbihan or Loir-et-Cher; whereas the total for Nagasaki, since data on only the first nine months of life are available, might be expected to range between the values for stillbirths-neonatal deaths and the totals for the two French areas. We note that the ratio of B to A obtained for Hiroshima compares favorably with those for Morbihan and Loir-et-Cher. Nagasaki, on the other hand, exhibits a value appreciably different from the other three areas. This is, of course, not unexpected in view of the discrepancies between Hiroshima and Nagasaki previously pointed out.

If one accepts the assumptions on which Morton, Crow, and Muller (1956) base their estimate of the total mutation rate for lethals and detrimentals in man, and if the differing periods of risk in Japan and France are taken into account, then the "total" rate of mutations in Hiroshima, for mutations expressing themselves in a fashion here measurable, would be substantially the same as those obtained by Morton, Crow, and Muller from the French data, namely, 0.03–0.06 mutants per gamete or $3\text{–}6 \times 10^{-6}$ per locus per generation. Nagasaki, however, would suggest a value only one-third to one-fourth as high. More reliable estimates of our "load of mutations" require (1) a better understanding of the average dominance of nominally recessive, deleterious genes in man, and (2) measurement of a wider spectrum of mutants than has thus far been possible in man. With regard to the former, our knowledge is so scanty that Morton, Crow, and Muller had to draw upon Drosophila data in order to estimate the mutation rate given above. Morton (personal communication) has indicated that the assumption that the average dominance of deleterious genes in man is the same as in Drosophila has been troublesome; moreover, even in Drosophila the data rest on a special class of recessives, namely, lethals. Efforts are currently underway to remedy the second deficiency enumerated by reinvestigating the children reported in this paper at ages 5–10. At this time, a wide battery of clinical, biochemical, anthropometric, and psychometric measures are to be obtained. It may be presumed that this more detailed examination of the children of consanguineous matings will reveal hitherto unmeasured genetic damage.

SUMMARY

Data on the effect of inbreeding on the sex ratio, and the frequencies of major congenital malformations, early deaths (stillbirths and neonatal deaths), deaths in the first nine months of life, and death in the first eight years of life have been pre-

sented. These data were collected in Hiroshima, Nagasaki, and Kure, Japan during the years 1948–1956 under the joint sponsorship of the Atomic Bomb Casualty Commission of the National Academy of Sciences-National Research Council of the United States and the National Institute of Health of Japan.

The prevalence of consanguineous marriages and the marriage practices which appear to maintain the relatively high degree of inbreeding in Japan are discussed. It is shown that consanguineous marriages vary in frequency and type in Hiroshima, Nagasaki, and Kure, and, at least with respect to Hiroshima and Nagasaki, the frequency of consanguineous marriages is clearly on the decline.

Among the socio-economic factors measured, consanguineous marriages do not differ significantly from non-consanguineous marriages with respect to economic level or frequency of positive serology among parturient mothers. Consanguineous marriages do differ significantly, however, from non-consanguineous marriages with regard to (1) maternal age, (2) parity, (3) paternal age, and (4) the frequency of "therapeutic" interruption of pregnancies.

Biological relationship of husband and wife does not appear to alter the effects of maternal age and parity on pregnancy outcome, nor can one demonstrate a significant effect of inbreeding on the sex ratio. Inbreeding does, however, significantly alter the frequency of major congenital malformations. Interestingly, a rather substantial portion of the increase in congenital malformations with increasing inbreeding is due to the occurrence of complex or multiple major malformations.

In these data, an unequivocal effect of inbreeding on early deaths cannot be demonstrated; this failure to demonstrate a consistent effect of inbreeding rests on demonstrable city heterogeneity. Hiroshima, Kure and Nagasaki are consistent in revealing an increasing death rate with increasing inbreeding; the heterogeneity arises in connection with the magnitude of this effect. Hiroshima and Nagasaki are in agreement in revealing an effect of inbreeding on mortality in the first 9 months of life, and Hiroshima reveals that this effect is still demonstrable after the first year of life.

No clear effect of inbreeding on the interval between cohabitation and the first recognizable pregnancy is demonstrable, and hence there is no evidence that the increased risk of homozygosity for deleterious genes among the children of related parents is manifested as early fetal loss and an apparent difficulty in establishing a successful pregnancy.

The results of this study are compared with the findings of other workers in Japan, and especially the findings of Sutter and Tabah in France. A general level of agreement is established.

ACKNOWLEDGMENTS

I am indebted to Drs. J. V. Neel and N. E. Morton for numerous helpful criticisms and suggestions in the preparation of this manuscript; and to Drs. N. Fujiki, K. Ohkura, and T. Yanase and Mr. H. Befu I extend my thanks for assistance in evaluating and interpreting the "Japanese scene". I am no less indebted to the personnel of ABCC, and the physicians, midwives, and inhabitants of Hiroshima, Kure, and Nagasaki without whose active support this study would not have been possible.

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Empirical Risks in Consanguineous Marriages: Birth Weight, Gestation Time, and Measurements of Infants[1]

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EXTENSIVE OBSERVATIONS on plants and animals support the generalization that increased morbidity and decreased size and vigor are the immediate effects of inbreeding on a normally outbred population. Genetic experiment and theory agree in attributing these results to the manifestation in a homozygous state of genes ordinarily heterozygous. An accumulated load of deleterious recessive mutations is inevitable in a cross-fertilizing species, and most inbreeding effects seem to be consequent on this. Other evidence indicates that selection sometimes favors the heterozygote over either homozygote, but the importance of such overdominance is poorly understood. For both mechanisms change in homozygosis is an appropriate measure of the inbreeding effect (East and Jones, 1919; Wright, 1921; Crow, 1952).

In man, cases of rare recessive diseases are often the issue of consanguineous marriage, and conversely, the frequent occurrence of parental consanguinity may be considered indirect evidence of a recessive component in diseases whose inheritance is uncertain. A comprehensive and reasonably restrictive estimate of inbreeding effects requires a large body of data and a relatively high incidence of consanguineous mating. Such material has recently become available through the genetics program of the Atomic Bomb Casualty Commission in Japan (Neel and Schull, 1956).

COLLECTION OF THE DATA

The data of this study have been collected as follows (Schull, 1958). During the years 1948–1954 in Hiroshima and Nagasaki, and 1948–1950 in Kure, a registration system for pregnant mothers was maintained in conjunction with the city offices responsible for the carrying out of rationing laws. Under this system, registrants reporting for special ration cards at about the fifth month of pregnancy were interviewed by Commission clerks, who obtained data on age, consanguinity, previous pregnancies, date of the last menstrual period, exposure to the atomic bombs, and other matters. At the time of birth of a child so registered, the cooperating midwife or physician reported on the onset and course of labor, sex, type of termination, and birth weight. Birth weight was determined after July, 1949, on scales distributed by the Commission, but before then on the attendants' own scales. Commission clerks computed gestation time from the registration record of the last menstrual period, if this had been ascertained. In an unknown fraction of the cases the date of

Received December 14, 1957.

[1] Genetics paper number 560. This work was sponsored by the Atomic Bomb Casualty Commission, Field Agency of the National Academy of Sciences-National Research Council, with funds supplied by the United States Atomic Energy Commission.

the last menstrual period was not known, but was taken from the attendants' records, or from the mother after the child was born, or rarely, estimated from the appearance of the baby. A Japanese physician in the employ of the Commission examined each baby, promptly if it was reported by the attendant to be abnormal, and usually within 2 or 3 weeks if the termination was reported normal. Consanguinity information obtained by the registration clerks was verified at this home visit. For all "abnormal" cases (as defined, these included nearly 20 per cent of all cases) and for a 10 per cent sample (those registration numbers ending in zero) a more detailed report was made, including the results of a test for maternal syphilis, gynecological history, a rating of economic status, and autopsy data, if any. In addition, a sample of infants surviving to the age of about 9 months was selected by the terminal registration number and examined in the clinic. For the study of infant measurements, age at examination has been restricted to 8, 9, and 10 months.

RELIABILITY OF THE CONSANGUINITY DATA

Evidence has been presented elsewhere that errors in determining degree of inbreeding may probably be neglected (Schull, 1958). There is reason to believe that techniques of measurement were unbiased with respect to consanguinity. Moreover, estimates of consanguinity effects from different cities and from midwives' and clinical data are in good agreement for all anthropometrics, and there is no indication of measurement bias with regard to exposure history which from the nature of the investigation was most subject to bias (Neel and Schull, 1956).

This does not imply, of course, that estimates of inbreeding effects from these data will necessarily be free from the extraneous effects of sociological concomitants of consanguineous marriage. Schull (1958) has reported that in this population consanguineous marriages were significantly associated with urban origin, nonexposure to the atomic bomb, a low incidence of induced abortions, a high number of conceptions, and low maternal age. Over the period of observation there has been a significant decrease in the reported incidence of consanguineous marriage. There was no association with birth injury or economic status as measured.

Even if consanguineous marriages do not differ from unrelated ones in unmeasured factors, the isolation of genetic effects from this tangle of sociological differences is uncertain. There is no indication of an association between radiation history and any of these anthropometrics (Neel and Schull, 1956). The effects of induced abortion have been eliminated as well as possible by excluding all known induced terminations. Stillbirths, neonatal deaths, and major congenital malformations have likewise been excluded. In addition to estimating the relation between inbreeding and defect from the pooled data, the material has been partitioned in different analyses by city, parity, radiation history, sex, age in months, and year of birth, and data from mothers negative for the syphilis test have been analysed separately for birth weight. None of these more detailed analyses gave estimates which differed appreciably from those obtained from the pooled data, and estimates of inbreeding effects from different degrees of consanguinity, omitting unrelated parents, agree with independent estimates from children of related and unrelated parents (table 2). Since any sociological concomitant of inbreeding might be expected to differ more between

children of related and unrelated parents than among different degrees of relationship, these observations suggest that, in this material, the estimates of genetic effects are not biased by extraneous factors.

ANALYSIS AND RESULTS

Schull (1958) gives the reported incidence of consanguineous parentage among the registrations for 1948–1954. Second cousins, first cousins once removed (1½ cousins), and first cousins account for nearly all cases ascertained, the remainder being largely composed of remote or unspecified relationships. In this material, ascertainment of consanguinity more remote than second cousins was not reliable, and only parents recorded as first cousins, 1½ cousins, second cousins, or unrelated have been used to estimate empirical risks. Parents are termed unrelated if they are not known to be related. Unless marriages of more remote relatives take place considerably more frequently than they would with random mating, and very much more frequently than our records indicate, the inbreeding coefficients of the four groups may be taken to be $\frac{1}{16}$, $\frac{1}{32}$, $\frac{1}{64}$, and 0, respectively (Wright, 1921).

The inbreeding coefficient (F) was defined by Wright so as to be proportional to reduction in heterozygosity. Insofar as selection and epistasis may be neglected, it is obvious from this definition that the inbreeding effect on the mean of a quantitative character is proportional to F:

$$m_F = m_0 - (m_0 - m_1)F$$

where m is the mean, $m_0 - m_1$ is estimated as a regression coefficient, and the subscripts 0, 1, and F denote no inbreeding, complete inbreeding and intermediate inbreeding, respectively (Wright, 1951). This approximation should give good results over small ranges of F, but for larger intervals deviations from linearity may become apparent, due to the damping or accelerating effects of selection and epistasis. As a test of linearity, the regressions for the three degrees of non-zero inbreeding (b_{FF}) and for inbred children vs. outbred children (b_{FO}) have been calculated in addition to the mean $\bar{b}$. Over the observed range of inbreeding from 0 to $\frac{1}{16}$, the two independent estimates agree closely for all the measurements of the present study (table 2), but there is little basis for estimating how important deviations from linearity might be if higher values of F could be observed.

Prima-facie evidence for inbreeding effects is given in table 1 as the pooled numbers of observations and means for the six measurements. For birth weight there is a slight decrease with inbreeding, and with more than 70,000 observations this is significant even when the unrelated group is excluded. Length of gestation, with almost the same number of observations, shows no effect of inbreeding. The gestation time of normal infants may well be determined by maternal characteristics, in which case it would not be expected to respond to inbreeding of the fetus. Inbreeding decline in the measurements of 8, 9, and 10 months infants is highly significant for weight and height. These conclusions are reinforced by the more detailed analysis within parity, city, age, and sex, by which analysis the effect of inbreeding on chest girth is also highly significant (table 2). Estimates from the three cities are homogeneous. There is no significant effect of inbreeding on the variances of individuals

TABLE 1. POOLED DATA ON INFANT MEASUREMENTS AND RELATIONSHIP OF PARENTS

	Unrelated	second cousins	1½ cousins	first cousins
		Means		
Weight of live births (dkg.)	307.4	307.1	307.1	304.6
Length of gestation (wks.)	40.13	40.22	40.11	40.13
Weight at 8–10 months (dkg.)	781.8	778.5	776.5	772.2
Height at 8–10 months (mm.)	689.6	689.3	689.8	687.3
Head girth at 8–10 months (mm.)	442.8	444.0	442.5	442.8
Chest girth at 8–10 months (mm.)	427.7	427.6	428.3	426.8
		Number of Observations		
Birth weight	70088	1252	892	2928
Gestation	58605	1058	766	2517
Metrics at 8–10 months	18501	330	244	815
		Inbreeding Coefficient		
	0	1/64	1/32	1/16

TABLE 2. REGRESSION COEFFICIENTS OF INFANT MEASUREMENTS ON INBREEDING (F) AND THEIR STANDARD ERRORS

	Pooled data	Within groups*		
	$\bar{b}$	b_{FO}	b_{FF}	$\bar{b}$
Weight of live births (dkg.)	−42 ± 12	−55 ± 13	−51 ± 29	−54 ± 12
Length of gestation (wks.)	.01 ± .70	.24 ± .78	−1.6 ± 1.7	−.10 ± .70
Weight at 8–10 months (dkg.)	−156 ± 50	−121 ± 53	−114 ± 117	−120 ± 48
Height at 8–10 months (mm.)	−34 ± 14	−24 ± 14	−46 ± 31	−28 ± 13
Head girth at 8–10 months (mm.)	1 ± 8	−7 ± 8	−25 ± 17	−10 ± 7
Chest girth at 8–10 months (mm.)	−12 ± 11	−28 ± 11	−33 ± 25	−29 ± 10

* The groups are city × parity × year for birth weight, city × parity for length of gestation, and city × sex × age in months for other measurements.

TABLE 3. REGRESSION OF THE WITHIN-GROUP VARIANCE OF INDIVIDUALS ON F, WITH THE STANDARD ERROR OF THE REGRESSION COEFFICIENT

	$\sigma^2 + bF$	s_b
Weight of live births (dkg.)	1750 − 177 F	736
Length of gestation (wks.)	5.0 − 1.0 F	2.3
Weight at 8–10 months (dkg.)	7500 + 9035 F	6337
Height at 8–10 months (mm.)	538 + 504 F	445
Head girth at 8–10 months (mm.)	158 + 153 F	132
Chest girth at 8–10 months (mm.)	351 + 464 F	297

(table 3), although these tend to increase with inbreeding as expected. A much larger series of observations would be required to estimate the genetic variance from the regression of the phenotypic variance on inbreeding (as sugsgeted by Hogben, 1933). The data are fully consistent with the hypothesis that inbreeding causes a decline in infant measurements, but the magnitude of this decline is extremely small and can be detected only in very large samples.

DISCUSSION

Some of the consequences of inbreeding in man may be deduced from the present estimates of genetic effects, assuming that these are unbiased. With regard to first-cousin marriages (F = .0625), the effect of inbreeding is estimated from $\bar{b}$ within groups (table 2) to be a decline of about 3.4 dkg. for birth weight, 7.5 dkg. for weight at 8–10 months, 1.8 mm. for height at 8–10 months, 1.8 mm. for chest girth at 8–10 months, and 0.6 mm. for head girth at 8–10 months. Such small decreases in body size must in themselves have only a slight, but perhaps not negligible, effect on infant survival. As for the effect of consanguineous marriages on infant size in the population, this is insignificant even in Japan, where consanguineous marriages are relatively common (Neel *et al.*, 1949). In our data, for example, the average inbreeding coefficient is .0031, or about 5 per cent as great as the inbreeding coefficient of first cousins, so that complete elimination of consanguineous marriages would have an effect on the population only 5 per cent as great as the effect of first-cousin parentage; decreasing the frequency of consanguineous marriage by a smaller amount, as Roman Catholicism has done for its adherents in Japan, would have a proportionately smaller effect (Schull, 1953).

Close consanguineous mating in human populations may be a less important form of inbreeding than isolation by distance or other barriers (Dahlberg, 1948). The magnitude of this inbreeding is difficult to assess, although Wright (1950) has suggested that it is not likely to be greater than F = .02, which corresponds to an isolate size of about 200 families. Accepting .02 as the maximum reduction in inbreeding brought about by increased dispersion in recent generations, it appears from table 2 that this "isolate-breaking" cannot account for an increase of much more than 1 dkg. in birth weight, 2 dkg. in weight at 8–10 months, and fractions of a millimeter in height, head girth, and chest girth at 8–10 months. Temporal changes in infant body size of greater magnitude than this must therefore be largely due to changes in nutrition or other environmental factors. Takahashi and Oshio (1938), comparing babies born at the Red Cross Hospital, Tokyo, in 1926–27 and again in 1937–38, observed an increase in birth weight of 7.4 $\pm$ 0.8 dkg., and in our own data for the postwar period 1949–1954, the increase in birth weight of children of unrelated parents, within parity and city, was 0.69 $\pm$ 0.12 dkg. per year. Ikuchi and Okuda (1927) compared Osaka babies examined in 1924–25 with Japanese standards published in 1902, and if the two groups are really comparable, it would appear that for babies at the age of 8–10 months, there had been an increase of several millimeters in height, head girth, and chest girth, and of more than 20 dkg. in weight, which is far too great to be attributed to isolate-breaking. This conclusion of course cannot be extrapolated to temporal changes in adult measurements, and inbreeding may have a greater effect on adult characteristics, as Dahlberg (1948) has suggested. However, there is no evidence that this is the case, and data on other mammals suggest no great increase of inbreeding effects with age, except perhaps for weight, which at birth is considerably influenced by maternal factors (Morton, 1955; Tyler, Chapman and Dickerson, 1949; Dickerson et al., 1954). It may be doubted, therefore, whether any appreciable fraction of the increase in size observed during recent generations in

Japanese and Western populations can be attributed to increase in heterozygosity through isolate-breaking.

SUMMARY

Offspring of unrelated parents, first cousins, first cousins once removed, and second cousins have been examined in three Japanese cities. The reliability and validity of the data are discussed. Taking account of city, parity, sex, and other relevant variables, the effects of inbreeding are estimated for birth weight, gestation time, and measurements of infants at the age of 8–10 months. For length of gestation and head girth no significant effect is detected. There is a small but significant decrease in weight, height, and chest girth with inbreeding. However, even for first-cousin matings the decrease in body size is slight. There is no significant effect of inbreeding on the variances of these measurements. The effects of "isolate-breaking" and of the prohibition of cousin marriage on body size are discussed, and it is concluded that these effects are likely to be quite small.

ACKNOWLEDGEMENTS

I am indebted to Drs. M. Kodani, W. J. Schull and K. Takeshima for assistance in securing these data and to Drs. A. B. Chapman, J. F. Crow, H. Maki and D. J. McDonald for helpful criticisms and suggestions.

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Genetic Variation in Tooth Dimensions: A Twin Study of the Permanent Anterior Teeth*

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THE RELATIVE indestructibility of the teeth make them important structures in tracing human evolution, and thereby provide valuable morphological characters for both paleontological and genetic studies (Lasker 1950). In human evolution, tooth size has been importantly reduced, particularly in the front portions of the jaws (Hooton 1947). An hereditary basis for differences in tooth size has long been assumed in dentistry (Kingsley 1888), and has received considerable support from twin and family evidence (Korkhaus 1930; Lundstrom 1948), as well as from odontometric population studies (Dahlberg 1945; Moorrees, et al., 1957). Because of the potential value of the teeth for genetic studies of quantitative variation and human evolution, a twin study method will be utilized here in an effort to further our understanding of the genetic control of variations in the dimensions of the permanent anterior teeth.

THE STUDY SAMPLE

The twin subjects in the present study are a part of a larger study which has been in progress for several years at the Columbia-Presbyterian Medical Center (Osborne 1956), and will be reported in detail elsewhere. The total study population was drawn from a variety of sources in New York City, unselected as to sex and zygosity, ranging in age from 18 to 55 years, and obtained for the purpose of establishing a population of adult twin subjects in good general health. From this twin population, subjects were given appointments to come into the Division of Research of the School of Dental and Oral Surgery of the Faculty of Medicine, Columbia University, where they were seen by one of us and complete dental examinations given (S. L. H.). The average age of the group so studied was 27 years and included 33 pairs of monozygotic twins (21 female and 12 male), 21 pairs of like sex dizygotic twins (16 female and 5 male). All subjects were Caucasian, predominantly of Northwest European descent, and approximately equally divided between Jews and Non-Jews.

METHODS

The diagnosis of twin zygosity has been based upon proving dizygosity, first by a proven difference in a blood group factor, and then by adding reliable morphological characters for those pairs agreeing in all factors tested for in extensive blood studies.

Received April 28, 1958.

* Prepared from a paper given in the American Society of Human Genetics Section of the American Institute of Biological Sciences meeting at Stanford University, August 26, 1957.

These criteria, as well as the method of diagnosis, will be presented in detail in a forthcoming publication.

For the measurement of the teeth quick setting stone casts were prepared from alginate impressions of the maxillary and mandibular teeth of each subject. Measurements of the widest mesio-distal diameter of each of the six maxillary and six mandibular anterior teeth of the permanent dentition were obtained from the models by means of a finely pointed sliding caliper, fitted with a vernier scale which permitted readings to the nearest 0.1 mm. The legs of the caliper were placed at the contact points and the instrument held parallel to the occlusal surfaces of the teeth as the individual tooth was measured. Teeth which had been restored with porcelain or acrylic jackets, and those which had either carious lesions or restorations which affected a contact point were eliminated from the study. All casts were given random code numbers, and measured individually, not as casts of twin pairs.

RESULTS

The first objective in a twin analysis is to test for the presence of a measurable component of genetic variability by comparison of the average of the differences between the two members of monozygotic twin pairs to the average of the differences between the two members of dizygotic twin pairs. This comparison has been made on the basis of the mean intrapair variances. The mean intrapair variance being $(\Sigma x^2)/2n$, where x is the difference between the two members of a twin pair for the mesio-distal tooth diameter of a given tooth, and n is equal to the number of twin pairs. From these mean intrapair variances, variance ratios have been calculated and the F Distribution used to obtain the probability level of these ratios. Heritability estimates have not been calculated because of reservations concerning both the genetic and statistical meaning of these estimates with twin data. Furthermore, heritability estimates yield no information of importance with human material which is not provided by the probability levels of the variance ratios.

To permit the assessment of measurement error, and to determine whether monozygotic intrapair variances demonstrate a measurable component of environmentally conditioned variability, a series of duplicate measurements were obtained. The models of 30 subjects were selected at random and duplicate measurements made of all the twelve teeth studied. A measurement error variance was calculated, where x is equal to the difference between the first and second measurements, and n is equal to the number of casts measured twice. The mean measurement error variances obtained ranged from 0.003 for the maxillary right central incisor to 0.008 for the maxillary right canine. In each instance, the mean measurement error variance is found to be significantly less ($P<.001$) than the monozygotic mean intrapair variance.

In orthodontic studies of tooth dimensions, where interest is mainly centered upon the amount of tooth material present, the average of the dimensions of the tooth on the right and left side is customarily used (Moorrees 1951). In genetic and anthropological studies it has been common practice to base the analysis on the teeth of one side. (Almost invariably a certain amount of asymmetry is present, and while this may be of considerable interest, it constitutes a special and extremely complex

problem). For our present purpose, the analysis is based entirely upon the teeth of the right side. The data for males and females were analyzed separately, but save for factors relating to assymmetry, there were no significant sex differences. In both Lunstrom's (1948) and Seipel's (1946) twin data no sex differences were found, therefore, in the present analysis males and females have been combined.

The mean intrapair variances of monozygotic and dizygotic twin pairs, together with the ratios of these variances, are presented in table 1. The strong genetic component of variability for mesio-distal tooth dimensions, particularly for the incisors, is in agreement with the findings of Lundstrom (1948), Korkhaus (1930), and others. The relatively large mean dizygotic variance of the maxillary lateral incisors is also in agreement with the previous twin data. The comparatively small component of genetic variability for the maxillary canines accords well with odontometric population data. The monozygotic, or non-genetic, variance of the maxillary canine is similar to that of the incisors, while the dizygotic variance is considerably smaller. The apparently lower genetic variability for the canines is compatible with the hypothesis of their relative stability in human evolution as suggested by Dahlberg (1949) in his adaptation of Butler's "field concept".

It has been well established that certain points in the dentition are more variable than are others (Moorrees 1957). In view of the apparently strong genetic component

TABLE 1. MONOZYGOTIC AND DIZYGOTIC MEAN INTRAPAIR DIFFERENCES IN MESIO-DISTAL CROWN DIAMETERS OF THE PERMANENT ANTERIOR TEETH†

	n	Variance	F Ratio
	a. Right Maxillary		
I_1			
MZ	30	.035	3.51**
DZ	18	.123	
I_2			
MZ	29	.038	8.50***
DZ	18	.323	
C			
MZ	29	.039	2.23*
DZ	18	.087	
	b. Right Mandibular		
I_1			
MZ	26	.015	5.53***
DZ	15	.083	
I_2			
MZ	29	.018	6.17***
DZ	17	.111	
C			
MZ	29	.030	3.27**
DZ	19	.098	

* $P < .05$; ** $P < .01$; *** $P < .001$.
† Males and females combined.

of variability for mesio-distal dimensions, the interrelationship of the dimensions of the permanent anterior teeth would be of interest. When the different teeth are studied within the same individual it is exceedingly difficult to analyze the true nature of their interrelationship because of the common environment to which they are subjected. By a modification of the twin method, however, it becomes possible to determine to what extent different traits or measurements, (in this instance mesio-distal tooth dimensions), are independent, mechanically, physiologically, or genetically (Lerner 1950). This modified twin method will be referred to as a "cross twin analysis". By this method the interrelationship between two teeth in the same individual can be compared to the interrelationship between one of these teeth in Twin A and the other tooth in Twin B, the co-twin. In the present study one member of each twin pair has been taken at random and his central incisor (I_1) compared to his lateral incisor (I_2) and the lateral incisor then compared to the canine (C) to determine the relationship between adjacent teeth within the same individual. The central incisor of the individual taken at random has then been compared to the lateral incisor of the co-twin, and the lateral incisor to the co-twin's canine for the cross twin analysis.

In monozygotic twins the cross twin values provide a measure of the importance of factors acting alike upon morphologically adjacent teeth in two different, though genetically identical, individuals. Comparison of the cross twin results to those obtained within individuals provides a measure of the relative importance of the within individual environment. A comparable analysis in dizygotic twins tests the "co-relation" or mutuality of relationship between these teeth in genetically different individuals. Comparison of the latter with the observations made within individuals and between the two members of monozygotic pairs indicates the relative importance of the genetic factors which are acting alike upon the mesio-distal diameters of adjacent teeth.

The correlation coefficient is an appropriate method for measuring the "co-relation" or association between two variates and has been employed here. To assure reliability of results by this method certain precautions have been taken. (i) The only comparisons made are those which previous odontometric and developmental studies have indicated to be meaningful. The correlation coefficient has not been used as a method of searching for statistically significant associations. (ii) Conclusions have been based upon the value of the calculated probabilities, rather than upon the magnitude of the correlation coefficient or their standard errors (Fisher 1954, p. 195). (iii) Interpretation as to the relative importance of the correlations of different sizes is based upon values of z, rather than upon values of r (Fisher 1954, p. 201).

In both maxilla and mandible the individual and the monozygotic cross twin correlations between adjacent teeth are highly significant (table 2). From this it is clear that large central incisors tend to go with large lateral incisors, and large lateral incisors tend to go with large canines. The fact that all the monozygotic cross twin correlations are highly significant further indicates that the association between adjacent teeth for mesio-distal dimensions is not merely a consequence of within individual mechanical or physiological influences. The comparability of the individual and monozygotic cross twin z values supports this conclusion. While the

TABLE 2. CORRELATIONS BETWEEN THE MESIO-DISTAL CROWN DIMENSIONS OF THE PERMANENT ANTERIOR TEETH

	Comparison	n	r	t†
	a. Right Maxillary			
	I_1 with I_2			
MZ	Individual	27	0.546**	0.850
	Cross Twin	28	0.694***	1.384
DZ	Cross Twin	20	0.397	2.270*
	Individual	20	0.834***	
	I_2 with C			
MZ	Individual	27	0.692***	0.671
	Cross Twin	28	0.578**	0.886
DZ	Cross Twin	17	0.349	1.792
	Individual	20	0.766***	
	b. Right Mandibular			
	I_1 with I_2			
MZ	Individual	26	0.803***	0.075
	Cross Twin	26	0.795***	0.949
DZ	Cross Twin	18	0.647**	1.205
	Individual	18	0.837***	
	I_2 with C			
MZ	Individual	28	0.850***	0.502
	Cross Twin	29	0.806***	3.030**
DZ	Cross Twin	17	0.116	1.551
	Individual	20	0.589**	

* $P < .05$; ** $P < .01$; *** $P < .001$.
† t is calculated for the difference of the values of z.

smallest z values are consistently obtained in the dizygotic cross twin correlations the dizygotic cross twin correlation of mandibular central incisor with mandibular lateral incisor is statistically significant. Apparently there is either little genetic variability or independence of affect in the genetic factors acting upon the mandibular incisors. Again, comparison of z values gives support to the conclusions based upon the significance of the cross twin correlation coefficient.

The dizygotic cross twin correlation coefficients for maxillary I_1 with maxillary I_2, maxillary I_2 with maxillary C, and mandibular I_2 with mandibular C, are the only correlations which fail to reach statistical significance. These dizygotic cross twin correlations suggest that some genetically conditioned independence of mesiodistal dimensions may be present for these teeth, in addition to a common size factor as previously discussed. The relatively small z transformations obtained for these three dizygotic cross twin correlations are in agreement with such a suggestion. The statistically significant difference between the maxillary I_1:I_2 dizygotic cross twin and individual values ($P = 0.02 - 0.05$), and between the mandibular I_2:C monozygotic and dizygotic cross twin z values ($P = 0.002 - 0.005$) gives further evidence of some genetically conditioned independence of maxillary I_1 and I_2, and mandibular I_2 and C in addition to some size influence. While the z transformations for the maxillary lateral incisor and canine do not provide significant differences in the present

data, it is probable that these teeth are also partly independent in view of the z values obtained.

DISCUSSION

The present data confirm previous findings by Lundstrom and others of a strong genetic component of variability in mesio-distal tooth dimensions for the permanent anterior teeth, particularly for the four incisors studied. Some support is also given to the hypothesis of a relatively small genetic variability of the canines.

The statistically significant correlation coefficients within individuals, and also in the monozygotic cross twin comparisons, must be interpreted as indicating some genetic control of tooth size common to adjacent teeth, and perhaps even of general tooth size in the anterior dentition. The significant differences between the z transformations, as well as the correlations obtained in the dizygotic cross twin analysis gives evidence that other genetic factors are also affecting the mesio-distal diameters of the maxillary lateral incisor, and the maxillary and mandibular canines. The results of this cross twin analysis is of particular interest in light of the developmental history of the permanent anterior teeth as presented by Schour (1940, 1955). While initation of all the permanent anterior teeth begins at 5–6 months in utero, completion of size growth of the different teeth in this group occurs at different times. The maximum size of the maxillary central incisors and the mandibular central and lateral incisors is established by 3 to 4 months after birth, approximately one month later in the case of the canines, and not until 10–12 months after birth for the variable upper lateral incisors. The present analysis now gives evidence that the size of these teeth is under different genetic control. It is therefore possible that for these teeth there is an association of time, size, and genetic control. Not only may the anterior tooth dimensions provide genetic differences with a recorded time of developmental effect, but also, as the monozygotic twin intrapair differences show a measurable environmental component of variability it may be further possible to use the anterior tooth dimensions for studying specific growth disturbances in monozygotic twins (Price 1950).

SUMMARY

A strong component of genetic variability for the mesio-distal tooth dimensions of the permanent anterior teeth is confirmed by the present data. By the use of a cross twin analysis, support is obtained for a hypothesis of a genetic control for general tooth size, as well as for other genetic factors which in addition affect the size of the maxillary lateral incisors and the canines. Developmental evidence supporting this hypothesis is discussed.

ACKNOWLEDGEMENTS

The authors would like to thank Drs. Howard Levene, John W. Fertig, and Lelitt Sanghvi for their helpful discussions, and Dr. L. C. Dunn for reading the manuscript. This study was supported by the Commonwealth Fund of New York.

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BOOK REVIEWS

Symposium on Antibodies: Their Production and Mechanism of Action

SPONSORED BY THE BIOLOGY DIVISION, OAK RIDGE NATIONAL LABORATORY. Reprinted from the *Journal of Cellular and Comparative physiology*, 50, Supplement 1, Dec. 157. 361 + x pp. Wistar Institute, Phila.

THIS VOLUME represents the papers presented at the tenth of a series of conferences sponsored by the Biology Division of the Oak Ridge National Laboratory and the Division of Biology and Medicine of the Atomic Energy Commission. The conferences have in the past covered a wide range of topics, in many cases more or less closely related to radiation effects, and the present volume is the result of the desire to have a conference dealing with the stimulation of recovery from radiation damage by bone marrow transplantation. But as in the past, the conference was very wisely not limited to any such narrow field, and the present volume is exactly what its title implies, a symposium of papers dealing with the production of antibodies, their properties, and their mechanism of action. The authors represented are among the best and most active workers in this field, and no reader desirous of knowing the present status of fact and theory concerning antibodies can afford to ignore this symposium. In addition to the ten papers dealing with antibodies, there are six dealing more specifically with bone marrow transplantation.

There is of course no longer any need to apologize (if there ever was) for reviewing a book on antibodies in a journal of genetics. We live in an age in which scientific frontiers are melting away, and immunology and genetics in particular have a number of problems in common, notably the question of how DNA (or RNA) can contain and transmit the information which leads to the synthesis of proteins: enzymes, presumably, in the case of genetics, and antibodies in the case of immunology. The genetic reader will be amply rewarded for a perusal of the theories and data discussed in the present book.

At the Oak Ridge conferences free informal discussion is encouraged, and some of this is reproduced, more or less verbatim, here. The result is often to throw further light on the more formal presentations, and in some cases considerably to enliven the tone of the book. For instance, one participant remarks, in reply to a question, "... I am in the middle of a dilemma. Physical chemists do not recognize me as a physical chemist and immunologists do not recognize me as an immunologist. But my wife loves me anyway." This particular participant, one suspects, had his tongue a little in his cheek, for he is certainly aware that he is loved, not only by his wife, but by all immunologists, to whose science he has made outstanding contributions.

Many of the papers are illustrated by graphs and photographs, and most have bibliographies. The only index the book has is one of names, which of course is better than nothing. The volume is paper-bound, but printed in good type on good paper.

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Bone and Radiostrontium

BY ARNE ENGSTRÖM, ROLF BJÖRNERSTEDT, CARL-JOHAN CLEMEDSON AND ARNE NELSON. New York: John Wiley & Sons, Inc., 1958, pp. 139.

ONE MAY wonder at the purpose of this small book by Engström, a leader in the field of biophysical instrumentation, and three of his younger co-workers at the Karolinska Insti-

tute of Stockholm. The preface describes it as a review of the work at that Institute which bears on the problem of the accumulation of strontium in the skeleton. The title would lead one to expect a broader coverage of the subject, especially because of its topical importance and the reputation of the senior author. Instead, the book consists of a very uneven compilation of some of the authors' experimental work, some reviews of clinical and experimental work performed by others, and some calculations on dosage of beta emitters and theoretical conclusions covering the tolerable dose of strontium 90.

The book is small—139 pages of large print with copious illustrations, graphs and figures. A large segment of the book is devoted to the authors' techniques of microradiography and microinterferometry, including their technical and theoretical aspects. Since Engström is primarily responsible for the development of microradiography as a tool for the study of bone structure and metabolism, it is understandable that an authoritative treatment of this procedure should be included in the volume, but the details have appeared in journals and texts previously as have the experimental data cited. Techniques of microinterferometry are summarized and only a few experiments are cited, possibly because of the newness of the procedure, although from the broader aspects of biological experimentation, this type of instrumentation would seem to have wider application.

Another segment of the book is devoted to calculations concerning the dose rate distribution from beta emitters. Here, the authors have devised a theoretical model of spongy bone containing beta emitters with characteristics of strontium 90 and decay products. From the model, they calculate the dose to different parts of the bone and marrow and present equations expressing the limit to which they have been able to solve the general representation of dose rate of beta emitters in materials of different densities.

Two review chapters are also included. The first describes in satisfactory detail for general scientific readers the metabolism of strontium. The second, on bone salt and the ultra structure of bone crystals and collagen, does not find an easy correlation with the strontium problem, since data concerning the possible manners of inclusion of strontium in the structures are not discussed. Finally, one chapter is a summary of the authors' recent studies on the distribution of strontium 90 in the skeletons of rats. The minuteness of detail of techniques and data included would be more proper to an original article in a journal. The studies are autoradiographic for the most part.

The book ends with a four page summary in which is included a discussion of the tolerable body burden of strontium 90. This reviewer found this part of the book unsatisfactory for a variety of reasons. The evidence on which the calculations for tolerable body burden of strontium 90 are made certainly is not given in adequate detail. The evidence is considered only in relation to the production of bone sarcoma and then without pertinent available data. The leukemia problem is entirely ignored as are other possible osseous effects of radiation from strontium 90. Genetic effects are not within the scope of the book and are not mentioned. The type of consideration given to the vital question of maximal permissible dose or maximal permissible concentration is one which conveys an atmosphere of unsupported assertion. A more considered presentation of evidence with appropriate qualifications would have made these conclusions less open to criticism and indeed less dangerous from the point of view of misquotation and misinterpretation.

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Heredo-Retinopathia Congenitalis:Monohybrida Recessiva Autosomalis

By Carl Henry Alström and Olof Olson; 178 pages including preface, bibliography and pedigree charts. Translated by Erica Odelberg, Lund, Sweden: Berlingska Boktryckeriet, 1957.

This monograph contains "A genetical-statistical study" of a heretofore unrecognized ocular clinical syndrome characterized by: (1) defective visual acuity, usually observed in the first year of life, and (2) classified as retinochoroiditis, amaurosis, or amblyopia congenita.

This is an excellent study meriting the perusal of all ophthalmologists and geneticists. The meticulous method of study and the collaboration of medical disciplines particularly well illustrate an excellent execution of the careful determination of the confines of a specific clinical syndrome.

The study, written in the excellent style of similar Scandinavian genetic monographs, summarizes the findings made on a series of an entity termed heredoretinopathia by the authors. The constellation of features constituting the syndrome consist of the following:

(1) Defective central vision at or shortly after birth.

(2) Fixational nystagmus.

(3) Progressive and gradual decline of vision with increasing age.

(4) Absence of early ophthalmoscopic changes or merely "small pale spots in the retinal periphery."

(5) Slowly progressive areas of nonspecific disseminated chorioretinal atrophy. The optic nerve and retinal vasculature are only minimally involved and then late in the course of the disease.

(6) Loss of visual function precedes visible ophthalmoscopic changes.

(7) Progressive keratoconus and cataract (lamellar and posterior polar) are components of the syndrome.

(8) Electroretinographic studies are abnormal and suggest "neuroepithelial degeneration."

(9) Relative absence of other systemic or central nervous system disease.

(10) Analyses of the data, both by Hogben and Haldane's methods, support the conclusion that the mode of inheritance of the syndrome was autosomal recessive.

(11) The incidence of consanguinity, first cousins, was $16.2 \pm 3.6\%$.

(12) The gene was spread throughout Sweden but with varying frequency.

Doctors Alström and Olson are to be commended for this valuable contribution to the medico-genetic literature. It is regrettable that no artist drawings of the ophthalmoscopic findings could be obtained.

Science will await with interest further study, particularly anticipating histopathological specimens.

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Chronic Radiation Hazards, an Experimental Study With Fast Neutrons

By G. J. Heary, R. J. Munson and R. H. Mole, London and New York; Pergamon Press, 1957, Page 191. $7.50

This monograph describes in detail the experimental design, methods and results of an investigation of the biological effects produced in mice by chronic exposure to ionizing radiation. The rather thorough discussion of the dosimetry and of the many intricate problems in the assessment of biological effects is of special value to investigators in radiation biology. The pitfalls in the interpretation of effects produced by radiation at different dose rates are duly stressed as an important factor in the analysis of the data.

The relative biological effectiveness of fast neutrons as compared with gamma rays was determined from data on survival, organ and body weight, hematological effects and pathological studies. Three large groups of mice were exposed to (1) maximum dose of 6.4 rads weekly, (2) a medium dose of 0.54 rads weekly, and (3) a minimum dose of 0.19 rads weekly. The results are both informative and provocative. The high dose of 6.4 rads weekly clearly impairs fertility and shortens the life span without affecting the white blood cell count. The lower doses of 0.54 and 0.19 rads weekly appear to be not demonstrably different from each other or from the controls with respect to a statistically significant biological effect. It appears that a significant effect may be produced at a dose between 0.54 and 6.4 rads weekly. Unfortunately, the results are not extensive enough for further characterization of the dose response relationship. The importance of studying many parameters of effect which vary in magnitude at different radiation intensities is clearly described. During chronic radiation the variation in recovery as affected by dose rate, organ sensitivity and age is found to be a fundamental complicating problem in the analysis and comparison of experimental results.

The text material is useful for workers in the nuclear sciences and is an important reference for the future studies which are necessary for our evaluation and understanding of the biological effects of low level exposure to ionizing radiation.

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Natural Selection in Man

James N. Spuhler (Editor). Detroit: Wayne University Press, 1958, pp. 72, $3.50 (clothbound).

This elegant (and expensive for its size) book contains four papers read at the Wenner-Gren Supper Conference of April 12, 1957. The four papers appear at first sight to be entirely disparate. That of J. F. Crow presents a mathematical theory of the action of selection in Mendelian populations; Ph. Levine's is an analysis of data on the influence of the genes for the ABO blood groups on the incidence of Rh hemolitic disease; C. C. Coon has written a travelog of an anthropologist's journey around the world; and J. V. Neel discusses some human traits which are variously influenced by selection in primitive and civilized human populations. But all these papers show keen awareness of the importance, and indeed of urgency, of investigation of selective processes in human populations—a topic which until recently was surprisingly neglected in anthropology, human genetics, physiology, and medicine. It is this evident awareness which makes the appearance of this book a significant event.

It is legitimate, and in fact necessary in a little explored field, to construct working hypotheses to stimulate and guide the collection of data which, in the fullness of time, will

serve as the foundation of a more securely established knowledge. It is to the credit of the contributors to this book that they realize both the need for and the tentative nature of their speculations. Here are, for example, some of the ideas which occurred to Coon during his journey: "That malaria may play a selective role in keeping the Mongoloids above 4,000 feet [in the Himalayas] is no new idea to the Mongoloids themselves . . . . However, something else must operate to keep the Caucasoids below 14,000 feet. That factor may well be a lack of high altitude adaptation concerned with libido and oxygen transfer from mother to foetus; this is known by analogy from studies in Peru and Bolivia. Even among the altitude-adapted Tibetans, libido increases markedly on visits to an altitude of 4,000–7,000 feet." Neel certainly has not lost his customary minutely critical and cautious attitudes, yet he engages in the following speculation: "But if, as seems possible, the intelligence requirements for marriage are being pushed upwards, then the net effect of this trend would be to shift the fulcrum of this balance [balanced polymorphism with respect to the genetic determinants of intelligence] toward the upper end of the scale. Whether this would offset the effects of the lower marriage rates of the more educated is debatable. Thus, in considering the genetic implications of failure to marry, it seems likely that each society will require a separate balance sheet." In this reviewer's opinion, Neel has succeeded in stating clearly a problem of great importance for evaluation of the evolutionary perspectives of our species.

In a field of research which appears to be ready for rapid advances, divergence of opinion is expected and perhaps even salutary. One of the problems concerning which there exists such a divergence is the nature of the genetic loads carried in populations of sexual species, including man. The chief components of the genetic load are two. The mutational load consists of recurrent mutants which are harmful both when homozygous and when heterozygous. The balanced load (or segregation load as Crow prefers to call it) consists of genetic variants which increase the fitness of the heterozygote but decrease that of the homozygotes. It would obviously be important to estimate, even very roughly, the relative magnitudes of the mutational and the balanced loads. In a brilliant recent work of Morton, Crow, and Muller, the contents of which are summarized by Crow in the book under review, an attempt was made to arrive at such an estimate by examination of the effects of inbreeding in human populations. The investigators concluded that the mutational load in man is much greater than the balanced load. This conclusion was, however, based on the assumption that the balanced load consisted of genetic variants represented in the populations by only two alternatives (alleles) which produced superior heterozygotes. If that were so, the loss of fitness in a completely homozygous population would be only twice as great as in a panmictic one. In the book under review, Crow points out that with K alleles at a locus making the heterozygotes equally superior to the homozygotes, the loss of fitness due to complete homozygosis would be K times greater than it would be in a panmictic population.

This seems to make the problem of the magnitude of the mutational and balanced loads in human populations wholly indeterminate. Nevertheless, Crow concludes that the inbreeding effects in human populations "are due largely to 'ordinary' gene loci and not those maintained in polymorphic balance," and that "if the fitness is greatly decreased by inbreeding it is to that extent largely attributable to the mutation load rather than the segregational." Some recent work makes these conclusions questionable. Wallace found that the average effect of heterozygosis for mutations induced in a strain of Drosophila made homozygous for a certain chromosome is an increase in fitness. Heterotic alleles may evidently arise at many, perhaps at most, gene loci, not at just some exceptional loci. Studies on natural populations of several species of Drosophila have demonstrated the existence in them of multiple series of chromosomal variants maintained in these populations in a balanced state. From the standpoint of population dynamics these chromosomal variants

may be treated as series of multiple alleles. Most assuredly, these results obtained with Drosophila cannot be extrapolated directly to human populations; they are, however, sufficient to emphasize the need of caution in trying to exclude various alternative hypotheses bearing on the possible genetic structure of human population, and even more to emphasize the need of further studies on both human and animal populations.

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Mental Deficiency: In Relation to Problems of Genesis, Social and Occupational Consequences, Utilization, Control and Prevention

BY J. E. W. WALLIN. Brandon, Vermont: Journal of Clinical Psychology, 1956, pp. xv + 200, $5.00.

A WELL-KNOWN mental deficiency expert for almost fifty years, the author has made major contributions in the areas of diagnosis, education and prevention. The present volume is especially of interest because of its emphasis on the genetic and eugenic aspects and their effects on public health. Several chapters are devoted to such topics as the influence of heredity on intelligence, gene-specific types of mental defect, mutagens, and positive and negative eugenic measures. In addition, the control of the condition is related to the number, intellectual performance and socio-occupational level of the offspring as well as to the frequency of criminality, sex delinquency and alcoholism among defectives.

Probably because the author wanted to provide a supplementary source book, rather than a definitive text, he did not hesitate to include a mass of old and recent research data in those chapters devoted to major problems of the field. Despite his obvious endeavor to be concise, he occasionally becomes encyclopedic with some inevitable inaccuracy.

One of the unusual features of the monograph is the presentation of early researches in the language of their day. Much of the terminology is obsolete and a potential source of error on the part of students. The frequent lumping of mental deficiency with psychoses and neuroses is a particularly inappropriate echo of an earlier era.

One of the author's goals has been to present investigations bearing on misconceptions about the mentally defective, especially with regard to fertility and the socio-economic fitness and biological quality of their children. The results of numerous studies are offered in staccato fashion, some of which would seem to have been dispensable in favor of a fuller elaboration of the author's ideas.

The reviewer was particularly interested in the chapter dealing with constructive means for coping with a problem that has occasioned much pessimism. Although some of the author's favorable impressions of the usefulness of certain medical techniques in altering the state of defect may still be unsubstantiated, his considerable experience in the formulation of eugenic proposals, some of which became the basis for legislative action, lends added weight to the conclusions drawn. Fortunately, he never underrates the value of euthenics in enhancing the well-being and productiveness of a segment of our population which, in previous years, had little opportunity for making any positive contribution to society.

Mental deficiency is an extremely complex problem. The author has succeeded admirably in denoting some of the urgent problems in a field which historically has played the role of a stepchild in the interests of psychiatric and psychologic investigators.

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La Popolazione di Pavia Durante il Dominio Spagnolo

By G. Aleati. Universitá di Pavia. Facoltá di Scienze politiche, Istituto di Statistica, Pubblicazione N. 1. Milano: A. Giuffré, 1957. pag. 290 + VIII. Lit. 2000.

Introducing the XX Cold Spring Harbor symposium on population genetics, Th. Dobzhansky stated that "accumulation of observational and experimental data is the order of the day". As far as human population genetics is concerned it goes without saying that it is the observational data with which we have to work. The system of Mendelian populations composing the human species is an intricate one, and is certainly unique in that it is not studied by observers of another species, but by some of its own members.

The cultural heritage of man creates in this respect many disadvantages, but also some unique advantages. One such is the fact that man has always kept, more or less carefully, records of some of the parameters of the population structure. Most of these records are lost, others are incomplete. Even many modern records are not very informative for the population geneticist. It is a sad consideration that apparently we had to have the shock of the prospective damage to future generations caused by radiation, to realize the importance of a better knowledge of the structure of human populations.

While there are still students who apparently think that the best way to study the effect of radiation on human populations is to irradiate heavily, mice, flies and plants, it is now generally agreed among human geneticists, that a better understanding of the genetic and demographic structure of human populations should provide a basis for a discussion of the problem. In studying the dynamics of human populations it is not possible to avoid using "historical" data. Historians, demographers and human geneticists use three different languages, whose mutual understanding would bring advances in many aspects of these branches of human knowledge.

In this book Dr. Aleati has studied the structure of the population of Pavia (Lombardy, Italy) during the period 1570–1700, when the town, the ancient capital of the Lombard reign and later the residence and domain of the Visconti and Sforza duchies, was under Spanish rule. The estimated population size during this period varies between 12,000 and 20,000. To-day Pavia is a university town with a population of ca. 70,000, four colleges and, as readers of this Journal surely know, a group of excellent geneticists.

The sources of information, the Church books stored in the town archives, have been scrutinized by the author. Those acquainted with the hand-written Latin of these books will realize the amount of work and patience involved. The data are divided in "parrocchie", and the parish is still the administrative subdivision of the Catholic Church. The sources are: 1) *libri baptisorum*, which register the sex and name of the newborn, the name and the matrimonial state of the parents and the date of baptism. The illegitimate births are carefully recorded. 2) *libri mortuorum*, which were available only from the beginning of the 17th century, containing the sex, name and age of the deceased. 3) *libri matrimoniorum*, which unfortunately do not give the age of the partners nor the origin of a partner who did not belong to the parish. 4) *stati animarum*, which give the population composition by age of the whole parish at a certain time. These were largely incomplete and, since their compilation must have been troublesome, the degree of accuracy varies greatly from parish to parish.

The book can be divided into three parts. The first is an introduction to the problems, the second describes and discusses the population structure and dynamics and their correlation with the economic and social patterns of the town, the third is devoted to a critical

examination of the character and validity of the sources. Four appendices covering 120 pages contain the primary material tabulated in detail.

The purpose of the author, who is a student of economic history, was to correlate the demographic data with the historical and economic evidence of the same period and this he has achieved in a masterly way.

What the human geneticist will find most useful is the authoritative discussion of the methodology and the criticism of the sources of information for these types of studies and the detailed presentation of the actual data. In the appendices distributions of births by year, month and sex are given for all parishes. Distributions of death are given in a similar way and the number and monthly distribution of marriages are also included.

Multiple births were also registered and I have recently commented upon them in a note in "The Journal of Heredity".

The only regrettable omission concerns the registration of the marriages, when the special "dispensa" for consanguineous marriages have not been registered by the author.

Those who read Italian will enjoy the pleasant style in which the book is written and the interesting discussion on the historical and economic aspects of the research. But the value of the actual figures will repay also those who can read only the graphs and the neatly arranged tables.

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LETTERS TO THE EDITOR

Mendelian Terms in Modern Genetics—An Anachronism?

To the Editor May 10, 1958

Dear Sir:

Mendel originally applied the terms *dominant* and *recessive* to characters, not to genes, and found these two terms adequate to describe expression of the traits he studied. Usage has been modified by at least four subsequent advances in genetics. First, cytology shifted attention from behavior of the characters to behavior of the determiners. Second, instances came to light of blending or intermediate expression of unit characters in heterozygotes. Third, careful studies have shown that many apparently recessive mutations produce some effect in the heterozygote. Fourth, some diseases long regarded as dominant in man are now being found to have more severe manifestations in the rare homozygotes (1). In addition to these constant differences of expressivity between heterozygotes and homozygotes, terminology is complicated by parallel differences in penetrance and by individual variations in expressivity. Finally, pleiotropic genes may have both dominant and recessive effects.

Confusion has resulted at many points, especially in human genetics, and attempts to introduce precision are doing little to clarify the issues. The term *dominant* is being challenged as not accurately descriptive of any human diseases (2, 3), although its usefulness in pedigree analysis and in population studies is not denied. Some typical recessive diseases are yielding to advanced methods of heterozygote detection, and there is a resultant tendency to deny validity of the term *recessive* when used without qualification (2).

The heart of the trouble seems to be that the more we learn about any trait, the closer is the correspondence between genotype and our best description of the phenotype. This reduces, and may eventually eliminate, the possibility of one factor concealing the action of its alleles. Yet practical considerations mentioned above seem to demand retention of the dominant-recessive dichotomy for some purposes. To just what, in modern genetics, do we and can we apply Mendel's concept of dominance?

I suggest that the terms *dominant* and *recessive* apply, as Mendel applied them, to traits, not to genes, and to traits only when these are clearly, if arbitrarily, defined. Reduced penetrance and variable expressivity need not invalidate Mendel's terms; these concepts were developed just because they made possible the recognition of Mendelian phenomena, including dominance, in complex situations. The specification of individual variation and levels of expressivity supplements and preserves the dominant-recessive classification. In several years of observation, I have found no case that could not be clearly and accurately described in this way.

To take the human blood groups as a first example, we do not know what the ABO genes do, and it is unlikely that any one prevents primary action of another. It is nevertheless clear that agglutinability of a person's red cells with anti-A serum is dominant over inagglutinability; the O trait is recessive when defined in terms of agglutination with anti-A or anti-B serum and future discoveries are unlikely to alter this significantly. As a second example, if the sickling trait is defined as sickling detectable by the standard methods, it is dominant; sickle-cell anemia defined as clinical anemia with sickling and hemolytic crises is a recessive disease. For studies in which individuals are classified by hemoglobin types the terms dominant and recessive may lose their usefulness, but not their accuracy; the ability to synthesize hemoglobin S is transmitted in Mendelian dominant fashion *to all offspring of a homozygous parent* in a diallele cross. At the enzymatic level of analysis such a recessive trait is essentially "amorphic": absence of the dominant trait.

Diseases now said to show "intermediate expression" range from some in which all heterozygotes have rather serious pathology, to cases at the other extreme in which identification of heterozygotes is difficult or incomplete. Cases of the first sort can be represented with an explanatory phrase such as "dominant with more severe expression in homozygotes." The other type of trait might be described as "recessive with a (sometimes) detectable carrier state." The distinction between these two is simple and consistent once the trait is clearly defined.

When, as in sickle cell anemia, modifying genes at the same or different loci result in occasional disease in the heterozygotes, then just insofar as methods are available to demonstrate these modifiers the definition of the recessive disease can be refined to exclude the two-factor conditions. If the modifying genes are not known and the heterozygous and homozygous effects are alike, the modal pattern may still suggest dominance or recessiveness. But here the Mendelian dichotomy may indeed break down and, instead, the essential statistic is penetrance (4), particularly in heterozygotes. Probably few traits will have more than transient residence in this borderland.

Not infrequently a human disease is dominant in some families and recessive in others. In instances supported by extensive pedigrees, dominant and recessive forms probably represent different genes and even different loci, and in these cases Mendel's terms may appear to apply better to genes than to traits. But in the case of tuberous sclerosis, for example, it is as clear and correct to say that this is usually a dominant hereditary disease, as to say that its usual cause is a dominant gene. Future research will presumably disclose biochemical or anatomical differences between such dominant and recessive disease analogs, and at that time the trait definitions will diverge.

I do not propose that such expressions as "recessive mutation" should be eliminated; their meaning will sometimes be unmistakable. But I suggest that whenever confusion arises, thinking will be clarified and communication facilitated by strict treatment of dominance and recessiveness as properties of arbitrarily defined traits.

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Selective Survival in Dizygotic Twins—A Reply

To The Editor
Dear Sir:

In the June 1958 issue of this Journal a letter by H. Eldon Sutton appears in reference to our article entitled "Selective Survival in Dizygotic Twins in Relation to the ABO Blood Groups" (December 1957, Vol. 9: 321–330). In this letter Dr. Sutton discusses " . . . possible alternative explanations of the data". Because of a possible impression of a greater divergence of opinion than actually exists, we would like to add brief comment.

Recent obstetrical, serological and twin evidence suggested the possibility that selective survival in relation to the ABO blood group system could occur in dizygotic twins. Two published bodies of data were suitable for examining this possibility. These two serological studies, one by Schiff and Von Verschuer (*Z. Morph. Anthrop.* 32: 244–249, 1933) and the other by Gedda (*Studio dei Gemelli, Rome, Edizioni Orizzonte Medico*, 1951, p. 486), were found to be compatible with an hypothesis of some selection in relation to the ABO blood groups. Schiff and Von Verschuer give data for 244 dizygotic twin pairs, of which 156 were found to be concordant for ABO. We had calculated from this that 156 out of 244 twin pairs give 63.9 per cent concordant pairs; Dr. Sutton calculated a concordance of 64 per cent. Schiff and Von Verschuer point out, as discussed by Sutton, the 88 discordant pairs were counted twice for their calculations, thus giving them an observed discordancy of 53 per cent and a concordancy of 47 per cent. Their theoretical expected concordancy value for sibling pairs was 45.6 per cent; we stand corrected for our interpretation of how this was obtained.

As discussed by Schiff and Von Verschuer (*Klin. Wchnschr.* 10: 723–726, 1931), this theoretical sibling value was based upon population gene frequencies and then adjusted for comparison to their twin concordancy value of 47 per cent. The proper comparison is therefore with 47 per cent, and the agreement of their theoretical value for siblings " . . . with the observed value for sibling pairs in the present data" was thus coincidental. Gedda's data give admittedly small differences, but have value as they give actual observed differences in 93 sibling pairs, which he indicated show a difference between dizygotic twins and sibling pairs. While no claim of magnitude was made, it was stated that these two studies ". . . added support to a hypothesis of selective survival". This was also stated on the basis of the excess of Type O concordant pairs seen in the data of Schiff and Von Verschuer ". . . similar to the findings of the present study", and stressed in our discussion.

Two small unpublished bodies of twin data were kindly placed at the authors' disposal; one was referred to in Dr. Sutton's letter, and the other came from England. After careful consideration and consultation, neither was used. The former, as pointed out by Dr. Sutton, showed no excess of concordance; the latter provided as high a proportion of pairs concordant in ABO as the authors' own data. It was decided to base the analysis upon our own data with a discussion only of the published material.

If a loss of dizygotic twins is occurring in relation to the ABO blood groups, this would be reflected in the frequency of the ABO phenotypes in dizygotic twins. Use of gene frequencies calculated on the basis of the phenotypes of dizygotic twins, as done by Sutton, would then automatically reduce the difference between the observed and theoretical values, thus obscuring the effect of such a loss of dizygotic twins. The gene frequencies employed in the analysis were justified by comparing the phenotype frequencies, not of the dizygotic twins alone, but of the total study population, parents and siblings of the twins included.

Alternative explanations of the findings were discussed in our paper. An alternative suggested by Dr. Sutton is ". . . a differential tendency for twinning among the various blood types"; we had suggested ". . . an excess of Type O women having dizygotic twins". Whatever the eventual explanation, we heartily endorse Dr. Sutton's appeal for ". . . much more data than have been collected by the various investigators".

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(*Note:* Several of the papers in *Acta Genetica* are deferred to our December issue.)

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* Supported in part by the National Institutes of Health, grant number C-3874.

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